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INCIDENCE OF FATAL CORONARY DISEASE IN NONDIABETIC AND IN DIABETIC PERSONS

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THERE is a widespread impression that persons suffering from diabetes are more prone to have coronary disease than nondiabetic persons of corresponding age, but to our knowledge no extensive statistics supporting this impression have ever been published. We have therefore analyzed all of the postmortem records on file in the department of pathology of the University of Minnesota covering the period from 1910 through 1947. The number of postmortem examinations performed annually during this period increased from about 200 in 1910 to nearly 2,700 in 1947. The total number is 50,775. There were 49,593 nondiabetic and 1,182 diabetic subjects.

In the nondiabetic group there were 31,975 males and 17,618 females. The age distribution is shown in tables 1 and 2. Only those subjects of autopsies are listed as dying of coronary disease in whom both the clinical and the anatomic evidence indicated coronary disease as the major lesion. There were nearly as many with moderately severe coronary disease in whom death was due to some other cause; but these were not included.

In the nondiabetic males (table 1) it will be noted that there were no deaths from coronary disease in the first two decades of life and only 8 in the third. After the fifth decade the percentage of those whose deaths result from coronary disease does not increase with advancing age but remains about 10 per cent. In the nondiabetic females the incidence of deaths due to coronary disease is notably less than the incidence in males until the age of 70 years, after which it is about equal to that in the males. Among nondiabetic subjects of autopsies the ratio of males to females dying of coronary disease is about 5 to 3.

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It is shown in tables 1 and 2 that fatal coronary disease is about twice as frequent in diabetic as in nondiabetic males and three times as frequent in diabetic as in nondiabetic females. Among diabetic

TABLE 1.—*Coronary Disease in Nondiabetic and in Diabetic Males Examined Post Mortem*

Decade, Years	Nondiabetic Males	Coronary Disease		Diabetic Males	Coronary Disease	
		Number	Per Cent		Number	Per Cent
0-10	4,286	0	0	7	0	0
10-20	932	0	0	9	0	0
20-30	1,809	8	0.4	11	0	0
30-40	2,790	60	2.1	33	3	9.1
40-50	4,433	336	7.5	46	8	17.4
50-60	5,824	606	10.4	116	13	11.2
60-70	5,883	654	11.1	188	46	24.5
70-80	4,406	472	10.7	115	24	20.9
80-100	1,583	161	10.2	33	6	18.2
40-100	22,149	2,229	10	498	97	19.5

TABLE 2.—*Coronary Disease in Nondiabetic and in Diabetic Females Examined Post Mortem*

Decade, Years	Nondiabetic Females	Coronary Disease		Diabetic Females	Coronary Disease	
		Number	Per Cent		Number	Per Cent
0-10	3,121	0	0	2	0	0
10-20	799	2	0.25	12	0	0
20-30	1,584	0	0	28	0	0
30-40	1,843	4	0.2	36	1	3
40-50	2,158	19	0.9	51	5	10
50-60	2,469	90	3.6	134	17	12.7
60-70	2,525	178	7.0	199	34	17.1
70-80	2,205	225	10.2	129	33	25.6
80-100	914	88	9.5	33	6	18
40-80	10,271	600	5.8	546	95	17.4

persons the incidence of fatal coronary disease is almost as high in females as in males.

Diabetes therefore accelerates atherosclerosis of the coronary arteries, and it has a more pronounced effect in females than in males. About 4 per cent of deaths due to coronary disease in males and nearly 14 per cent in females are associated with diabetes.

PRIMARY ALVEOLAR CELL TUMORS OF THE LUNG

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TUMORS considered to arise from cells of the pulmonary alveoli are distinctly uncommon. On the basis of morphologic features such tumors may be divided into cancerous and noncancerous and into nodular and diffuse types. The noncancerous ones are usually referred to as pulmonary adenomatosis; the cancers are listed under the term "alveolar cell carcinoma."

The first report of bilateral pulmonary alveolar cell adenomatosis in man was that of Helly [1] in 1907. Since that time 14 other acceptable instances have been reported.[2] In 6 of the 15 cases the tumor was diffusely distributed, being unilateral in 2 and bilateral in 3. In the other 9 cases the tumor was of the diffuse type, involving all lobes of both lungs.

The multiple nodular type of alveolar cell carcinoma was first described by Malassez [3] in 1876. The diffuse type was first reported by Musser [4] in 1903. Since these cases were recorded, 26 other instances of alveolar cell carcinoma have been reported.[5] These, along

From the Departments of Pathology of Northwestern University and Wesley Memorial Hospital.

1. Helly, K.: Ztschr. f. Heilk. **28**:105, 1907.

2. (*a*) Löhlein, M.: Verhandl. d. deutsch. path. Gesellsch. **12**:111, 1908. (*b*) Gorden, A. K.: Lancet **2**:501, 1920. (*c*) Reuss, H.: Ueber Zwei Fälle multicentrisch entstandener Lungenkrebse, Inaug. Dissert., Hamburg, 1934. (*d*) Weissmann, S.: Frankfurt. Ztschr. f. Path. **47**:534, 1935. (*e*) Bonne, C.: Am. J. Cancer **35**:491, 1939. (*f*) Richardson, G. O.: J. Path. & Bact. **51**:297, 1940. (*g*) Sims, J. L.: Arch. Int. Med. **71**:403, 1943. (*h*) Bell, E. T.: Am. J. Path. **19**:901, 1943. (*i*) Taft, E. B., and Nickerson, D. A.: ibid. **20**:395, 1944 (2 cases). (*j*) Geever, E. F.; Carter, H. R.; Neubueger, K. T., and Schmidt, E. A.: Radiology **44**:319, 1945. (*k*) Wood, D. A., and Pierson, P. H.: Am. Rev. Tuberc. **51**:205, 1945. (*l*) Simon, M. A.: Am. J. Path. **23**:413, 1947. (*m*) Drymalski, G. W.; Thompson, J. R., and Sweany, H. C.: Am. J. Path. **24**:1083, 1948 (2 cases).

3. Malassez, L.: Arch. de physiol. norm. et path. **3**:353, 1876.

4. Musser, J. H.: Univ. Pennsylvania M. Bull. **16**:289, 1903.

5. (*a*) Finlay, D., and Parker, R. W.: Lancet **1**:838, 1877. (*b*) Kretschmer, W. H.: Ueber das primäre Bronchial- und Lungencarcinom, Inaug. Dissert., Leipzig, B. Georgi, 1904. (*c*) Pepere, A.: Centralbl. f. Path. **15**:948, 1904; cited

(Footnote continued on next page)

with the 2 cases reported in this paper, make a total of 30 instances of alveolar cell carcinoma of the lung. In all 30 cases the tumor involved both lungs. In 11 of these it was of the multiple nodular type; in 10 it was of the diffuse type, and in 9 there were both nodular and diffuse types of neoplasm in different parts of the lungs. Some of these cancerous growths produced metastases; others were invasive. In 25 cases there were extrapulmonary metastases; in 3 there was tumor within pulmonary vessels, and in 2 there was local invasion of interstitial tissue and pleura.

The number of cases of primary alveolar cell tumor accepted as authentic and their classification as "benign" or "malignant" vary in different reports. The evaluation of recorded cases is difficult because of incompleteness of microscopic descriptions, failure to exclude other organs as primary sites of tumor and the unwillingness of many authors to admit the alveolar cell origin of such tumors. As indicated by Neubuerger and Geever [6] in their review of this subject, there are many controversial and not completely acceptable cases that in all probability belong to cancerous and noncancerous groups. The morphologic features of pulmonary adenomatosis and alveolar cell carcinoma are so similar that it seems highly probable that they are related. Nevertheless, most of the reports deal either with pulmonary adenomatosis or with alveolar cell carcinoma, and in only a few, like those of Neubuerger and Geever [6] and Simon,[21] is the possibility of a relationship between the two conditions suggested. Both pulmonary adenomatosis and alveolar cell carcinoma occur in two distinct forms, i. e., multiple nodular and diffuse. As already indicated, both conditions are usually bilateral and involve all lobes of both lungs. The diffuse type of lesion has a gross appearance like that of lobar pneumonia in the stage of gray hepatization. Mucin may be produced in sufficiently

by Neubuerger and Geever.[6] (*d*) Knierim, H.: Verhandl. d. deutsch. path. Gesellsch. **13**:407, 1909. (*e*) Briese: Frankfurt. Ztschr. f. Path. **23**:48, 1920. (*f*) Schmincke, A.: Centralbl. f. Path. **33**:18, 1922; cited by Neubuerger and Geever.[6] (*g*) Gödel, A.: Frankfurt. Ztschr. f. Path. **29**:375, 1923. (*h*) Hedinger, E.: Schweiz. med. Wchnschr. **53**:165, 1923. (*i*) Rusk, G. Y., and Randolph, V.: J. A. M. A. **82**:442, 1924. (*j*) Fried, B. M.: Arch. Int. Med. **35**:1, 1925. (*k*) Oberndorfer, S.: Virchows Arch. f. path. Anat. **275**:728, 1930. (*l*) Sweany, H. C.: Arch. Path. **19**:203, 1935. (*m*) Graber, K.: Beitrag zur Histopathologie des primären Lungenkrebses, Inaug. Dissert., Munich, Speyer, Pilger, 1938; abstracted, Centralbl. f. Path. **77**:93, 1941. (*n*) Casilli, A. R., and White, H. J.: Am. J. Clin. Path. **10**:623, 1940. (*o*) Neubuerger, K. T.: J. Thoracic Surg. **10**:557, 1941. (*p*) Dacie J. V., and Hoyle, C.: Brit. J. Tuberc. **36**:158, 1942. (*q*) Wood, E. H.: Radiology **40**:193, 1943. (*r*) Geever and others [2j] (5 cases). (*s*) Drymalski and others.[2m]

6. Neubuerger, K. T., and Geever, E. F.: Arch. Path. **33**:551, 1942.

large amounts to be recognized grossly as a viscid translucent material in the affected portions of the lung; thus the gross picture may be confused with that of pneumonia caused by Friedländer's bacillus or Pneumococcus type III. The striking microscopic features of pulmonary adenomatosis are alveoli lined with epithelium-like cells, marked fibrosis and lymphocytic infiltration of interalveolar septums (fig. 1). The lining alveolar cells are columnar or cuboidal and usually nonciliated (fig. 2). They are uniform in size, shape and staining reaction. Mitotic figures are few, and there is no invasion of adjacent tissue. The nuclei are usually basally situated and homogeneous in appearance. The cytoplasm is eosinophilic and may be vacuolated. In some instances the cells are of goblet type. Mucin may be present within the lining alveolar cells and within the alveolar spaces (figs. 1 and 2). In some instances, however, mucin has not been satisfactorily demonstrated. The microscopic characteristics of alveolar cell carcinoma (figs. 5 and 6) are similar to those of adenomatosis—cellular pleomorphism, invasion and metastases being the contrasting differences. It should be noted that in the cases reported by Dacie and Hoyle [5p] and Wood,[5q] as well as in case 1 of this paper, the changes in all lobes of the lungs are like those of pulmonary adenomatosis except for small foci in a lobe of one lung, where there is demonstrable invasive carcinoma; these cases are considered to be examples of diffuse pulmonary adenomatosis with focal cancerous change. In 2 of the other cases classed as instances of cancerous pulmonary adenomatosis there was vascular invasion, and in the remaining 25 cases there were extrapulmonary metastases. It thus seems possible that pulmonary adenomatosis in man may be an early stage of alveolar carcinoma or that it may undergo cancerous change. The differentiation of alveolar cell adenomatosis and alveolar cell carcinoma on the basis of the cytologic aspects alone may be difficult (figs. 2 and 5). This is exemplified in the cases reported by Briese [5o] and Oberndorfer.[5k] In both instances the cases have been unjustifiably classed as instances of pulmonary adenomatosis in spite of the existence of extrapulmonary metastases.

The controversial question regarding the origin and the nature of alveolar lining cells still exists. Many authors, such as Bensley and Bensley,[7] Miller,[8] Bremer [9] and Cooper,[10] have maintained that the alveoli are lined by a continuous epithelial layer. Others, including

7. Bensley, R. D., and Bensley, S. H.: Anat. Rec. **64**:41, 1935.

8. Miller, W. S.: The Lung, Springfield, Ill., Charles C Thomas, Publisher, 1937.

9. Bremer, J. L.: Contrib. Embryol. **25**:83, 1935.

10. Cooper, E. R. A.: J. Path. & Bact. **47**:105, 1938.

Maximow and Bloom,[11] Lang,[12] Rose,[13] Fried[14] and Loosli,[15] have considered the lining alveolar cells to be mesenchymal. Still others, like Ross,[16] have expressed the belief that both mesenchymal and epithelial cells line the alveoli, and Bell [22b] indicated that occasional epithelial cells may be found in postnatal lungs. This problem has still to be definitely settled, but in view of the work of Oppenheimer[17] suggesting the possibility of mesenchymal cells giving rise to epithelium-like cellular elements it may be less important than was formerly thought. In none of the acceptable reported cases of alveolar cell tumor of human beings can a bronchial focus be demonstrated. In many instances the tumor appears to be multicentric in origin and to arise directly from alveolar walls. The tumor cells are usually not ciliated and are not continuous with bronchiolar epithelium. The morphologic features of the tumor cells and the fact that they produce mucin indicate that they are of epithelial type. At the present time it cannot be stated with certainty whether these cells originate from preexisting epithelial cells or as a result of metaplasia of an indifferent type of mesenchymal cell. The fact that in case 1 some of the cells lining alveoli have distinct cilia (fig. 2) could be used to support the contention that such cells, at least in this instance, are bronchiolar or bronchial in origin.

These tumors of human beings are also of interest because of certain similarities particularly of the "benign" type to a pulmonary lesion of sheep,[18] mice,[19] horses[20] and guinea pigs.[21] That the condition occurs in sheep has been known since about 1891. It has been referred to as jagziekte, epizootic adenomatosis, pulmonary adenomatosis and infectious adenomatosis. Very similar and probably identical conditions have been reported under the titles of verminous pneumonia[22a] and Montana progressive pneumonia[23] of sheep. The disease of sheep has

11. Maximow, A., and Bloom, W. A.: A Textbook of Histology, Philadelphia, W. B. Saunders Company, 1930.
12. Lang, F. J.: J. Infect. Dis. **37**:430, 1935.
13. Rose, S. B.: Arch. Path. **6**:36, 1928.
14. Fried, B. M.: Medicine **10**:373, 1931.
15. Loosli, C. G.: Am. J. Anat. **62**:375, 1937.
16. Ross, I. S.: Arch. Path. **27**:478, 1939.
17. Oppenheimer, J.: Quart. Rev. Biol. **15**:1, 1940.
18. Cowdry, E. V.: J. Exper. Med. **42**:323 and 334, 1925.
19. Tyzzer, E. E.: J. M. Research **17**:155, 1907.
20. Theiler, A.: Jaagsiekte in Horses, in Seventh and Eighth Reports of the Director of Veterinary Research, Department of Agriculture, Union of South Africa, April 1918, p. 59.
21. Grumbach, A.: Bull. Assoc. franç. p. l'étude du cancer **15**:212, 1926.
22. Dungal, N.: (*a*) Proc. Roy. Soc. Med. **31**:497, 1937; (*b*) Am. J. Path. **22**:737, 1946.
23. Cowdry, E. V., and Marsh, H.: J. Exper. Med. **45**:571, 1927.

been reported in widely scattered parts of the world, such as South Africa, England, Iceland, Germany and Montana. In such localities it has been responsible for marked economic losses, some farms having lost 50 to 85 per cent of their flocks because of this disease. The name jagziekte is derived from the Dutch words *jagt,* to drive, and *ziekte,* sickness, and is intended to indicate that the first symptoms appear in animals that are fatigued as a result of having been driven a long distance. The exact cause of the disease is unknown, but it is commonly believed to be infectious and capable of epidemic spread. Many workers hold that it is of viral origin, which is supported but not completely established by the work of Dungal.[22b] Neither the possibility of its being a nonspecific response to irritants as suggested by Grumbach [21] nor the idea of De Kock [24] that it is a true neoplasm can be excluded. The latter view is supported by Aynaud's [25] report of an instance in which pulmonary adenomatosis of a sheep had metastasized to regional lymph nodes.

The gross and microscopic features of the disease of sheep are similar to those noted in human cases of "benign" alveolar cell tumors. Thus, in sheep the lesions are usually extensive in both lungs, the normal pulmonary structure is retained, lining alveolar cells are of cuboidal or columnar type, proliferation and lymphocytic infiltration of interstitial tissue are impressive, and, with the exception of the case reported by Aynaud,[25] invasion and metastases are absent. There are usually minor differences in the appearance of the epithelial cells, but the morphologic similarities are striking. Nevertheless, at present the belief that there is a significant relation between the disease of sheep and the alveolar cell tumors of human beings is speculative and not clearly established.

REPORT OF CASES

Case 1.—L. W., a white woman aged 51 years, was admitted to Wesley Memorial Hospital first on July 10, 1947 with complaints of difficulty of breathing, cough and weakness. Her breathing had become progressively labored since one year before; at the time of hospitalization climbing one flight of stairs produced marked dyspnea and discomfort. The cough began three months before admission; it was nonproductive and frequently was nocturnal and paroxysmal, so that she could not sleep. There was no history of hemoptysis, cyanosis, pain of the chest or orthopnea. The patient had lost approximately 15 pounds (7 Kg.) in weight during the previous three months. She also complained of loss of appetite, diarrhea and weakness of a few weeks' duration. On admission her temperature was 98 F.; pulse rate, 80; respiratory rate, 34; blood pressure, 120 systolic and 80 diastolic. She was cyanotic and breathing rapidly, with effort, the veins of the neck distended.

24. De Kock, G., in Annual Report of the Director of Veterinary Service, Department of Agriculture, Union of South Africa, 1929, vol. 2, sect. v-ix, pp. 611 and 1169-1183.

25. Aynaud, M.: Compt. rend. Soc. de biol. **95**:1540, 1926.

There was a male distribution of hair over the chest, abdomen and pubis; the breasts were normal. The left border of the heart was in the fifth intercostal space and midclavicular line, with no murmurs or thrills; gallop rhythm was noted. The lungs showed diminished resonance to percussion, and loud inspiratory rales were heard over the lower lobes posteriorly. In the abdomen the liver was palpable 2 cm. below the right costal margin; there were no masses or tenderness. The nail beds of the extremities were cyanotic; there was 2 plus pitting edema of the lower legs. Laboratory examination showed: 300 mg. of albumin and 1 to 3 white blood cells in the urine; 4,030,000 erythrocytes and 9,200 white cells per cubic millimeter of blood; 14 Gm. of hemoglobin per hundred grams of blood; a negative Wassermann reaction of the blood; an erythrocyte sedimentation rate of 18 mm. per hour; nonprotein nitrogen 55.6 mg., albumin 2.56 Gm. and globulin 3.57 Gm. per hundred cubic centimeters of blood; an electrocardiographic pattern characteristic of right-sided heart strain; roentgen evidence of a 15 per cent enlargement of the cardiac silhouette and slight passive congestion of the lungs.

The patient was placed at rest in bed and treated with nasally administered oxygen, digitoxin and ammonium chloride. Her symptoms and signs became less marked, and her nonprotein nitrogen was 35.5 mg. per hundred cubic centimeters on the nineteenth hospital day. Slight dyspnea and cyanosis persisted, and she was discharged on the forty-third hospital day.

The patient was readmitted to the hospital on Sept. 25, 1947. At this time she complained of marked difficulty in breathing, of gaining 30 pounds (13.5 Kg.) in four weeks and of "shingles" of the left side of the chest. Her temperature was 97.8 F.; pulse rate, 96; respiratory rate, 40; blood pressure, 110 systolic and 90 diastolic. There were marked cyanosis, dyspnea and orthopnea. The left border of the heart was in the anterior axillary line; the pulmonic second sound was accentuated, being much louder than the aortic second sound. The lungs had coarse moist rales throughout the lower lobes. In the abdomen the liver was palpable 1½ fingerbreadths below the right costal margin; there was ascites of moderate degree. The lower extremities showed 4 plus pitting edema extending up to the middle of the thighs. Laboratory examination showed: 300 mg. of albumin in the urine; red blood cells, 4,900,000, with 15.5 Gm. of hemoglobin; white blood cells, 16,500, 91 per cent of which were neutrophilic granulocytes and 9 per cent lymphocytes; chlorides 413 mg., nonprotein nitrogen 41.7 mg., albumin 2.31 Gm. and globulin 4.23 Gm. per hundred cubic centimeters of blood.

The patient's condition became progressively worse, and she died on her third hospital day. The clinical diagnosis was Ayerza's disease.

Autopsy (C. I. Fisher, M.D.) revealed: hypertrophy and dilatation of the right atrium and the right ventricle; marked sclerosis of pulmonary arteries and arterioles; bilateral acute fibrinous pleuritis; bilateral acute bronchopneumonia; diffuse alveolar cell tumor involving both lungs and invading the interstitial tissue and the visceral pleura of the lower lobe of the right lung; herpes zoster of the skin of the left side of the thorax; moderate arterial and arteriolar nephrosclerosis; ascites (1,400 cc.); moderate edema of the lower extremities.

The heart weighed 305 Gm. The hypertrophy was limited to the right atrium and the right ventricle. The wall of the right ventricle, in spite of marked dilatation of the chamber, measured 8 mm. in thickness.

The right and left lungs weighed 800 and 600 Gm., respectively. All lobes of the lungs were increased in size and showed uniformly increased consistence. Crepitation was greatly reduced. The cut surfaces were homogeneous and pale gray mottled with black. In the peripheral and posterior portion of the lower lobe

of the right lung there were two spherical, firm, pale yellowish gray nodules with maximum measurements of 0.9 and 2.0 cm. These nodules had no demonstrable connection with bronchi. Numerous microscopic sections of all lobes of the lungs revealed an impressive increase in the amount of interstitial connective tissue, in which there were many lymphocytes and plasma cells (fig. 1). The alveoli were lined with ciliated high columnar cells of epithelial type (fig. 2). Some of these cells, as well as the alveoli, contained material which stained positively for mucin by the mucicarmine method. The two nodules in the lower lobe of the right lung were made up of richly cellular, pleomorphic, invasive neoplasm that formed glands and mucin (figs. 3 and 4). Throughout both lungs the microscopic features were like those of pulmonary adenomatosis, and in the circumscribed nodules in the lower lobe of the right lung they were those of invasive adenocarcinoma. No metastatic tumor was demonstrated in either regional lymph nodes or other viscera. A complete autopsy was performed and no other site of primary tumor was demonstrated.

Sclerosis was slight in the large pulmonary arteries but striking in the small pulmonary arteries and arterioles. Many of the sclerotic vessels showed intense lymphocytic infiltration, particularly of the thickened intimal portions.

CASE 2.—A. D., a 45 year old white man, was admitted to Wesley Memorial Hospital on May 4, 1948. His chief complaint was pain in the chest on coughing, of nine months' duration. During the month preceding hospitalization he had noted hemoptysis, shortness of breath, loss of appetite and an increase in the severity of the thoracic pain. For a few days before admission the pain radiated from the back to the front of the chest on the left side and was brought on by deep inspiration or sudden movement of his back. During the course of his present illness he had been treated for "arthritis of the spine." He estimated that he had lost 25 pounds (11 Kg.) since the onset of his illness. On the evening prior to admission, after an attack of coughing, he noted severe pain in the left dorsal region, which persisted and prevented him from sleeping. His past history was noncontributory. On admission his height was 5 feet 9 inches (175 cm.); weight, 140 pounds (63.5 Kg.); temperature, 100 F.; pulse rate, 156; respiratory rate, 44; blood pressure 120 systolic and 80 diastolic. In appearance he was well developed, moderately undernourished, pale, slightly cyanotic and evidently in pain. In the neck, in the supraclavicular region, bilaterally, there were several firm, discrete, nontender lymph nodes measuring 1 to 2.5 cm. in maximum measurement. The heart was not enlarged to percussion, and there were no murmurs or abnormal rhythm. The thorax was symmetric. Its expansion was markedly limited, and there were tenderness posterolaterally on the left, dulness at the bases of the lungs posteriorly, bronchial breathing and coarse rales laterally at the base of the left lung. Back motion was limited because of pain in the thoracic region; the remainder of the examination revealed nothing of significance.

At admission the urine was normal. The blood showed 5,400,000 erythrocytes and 30,500 white cells (92 per cent neutrophilic granulocytes, 8 per cent lymphocytes); the hemoglobin content was 16 Gm., the hematocrit reading 46; a blood culture was negative; the blood nonprotein nitrogen was 40.3 mg. per hundred cubic centimeters. Seven examinations of sputum revealed no acid-fast bacilli. Roentgen examination showed: 30 per cent enlargement of the cardiac silhouette; mediastinal enlargement, probably due to lymphadenopathy; diffuse mottling due to small areas of increased density in all lobes of the lungs, particularly in the central region and in the lower lobes; slight atelectasis of the middle lobe of the right lung; the left leaf of the diaphragm slightly higher than the right.

Three days after hospitalization the white blood cell count was 9,950, with 88 per cent neutrophils and 12 per cent lymphocytes. For thirteen days he showed symptomatic improvement, becoming less cyanotic and less dyspneic. A roentgenogram of the chest at this time showed no noteworthy change. On his

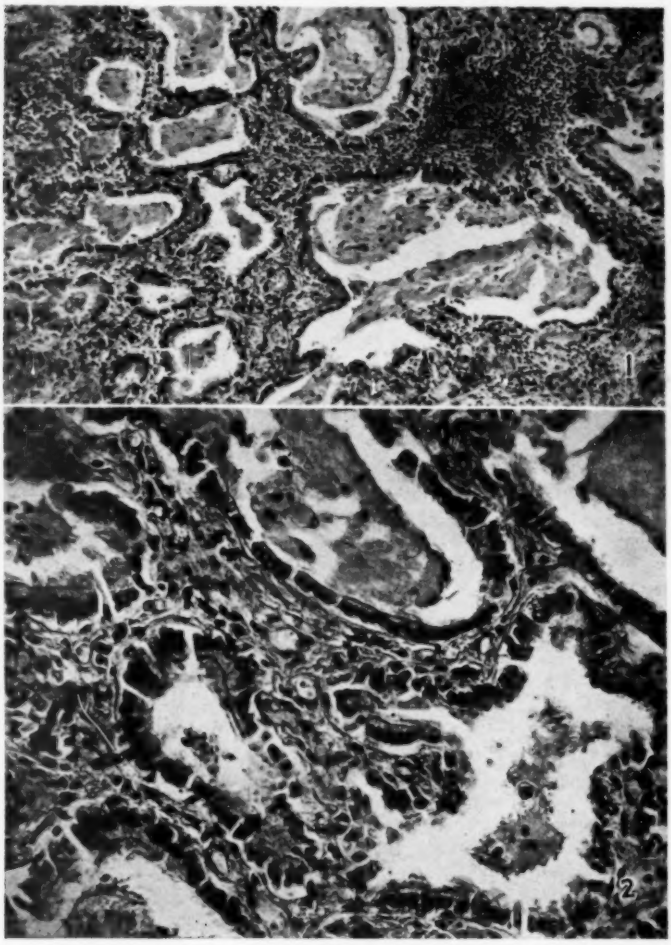

Fig. 1 (case 1).—Alveoli of the upper lobe of the left lung; × 290. They contain mucin and are lined with high columnar cells. The interstitial tissue is increased in amount and infiltrated by lymphocytes.

Fig. 2 (case 1).—Alveoli of the upper lobe of the left lung; × 550. They are lined with high columnar cells of mucin-secreting type. No noteworthy cellular pleomorphism is evident. A few of the cells have identifiable cilia.

fourteenth hospital day he noted severe pain in the left side of his chest with marked dyspnea, cyanosis and tachycardia. Two days later, shortly after precordial pain, cyanosis and pink sputum had been noted, gasping respirations developed and the patient died.

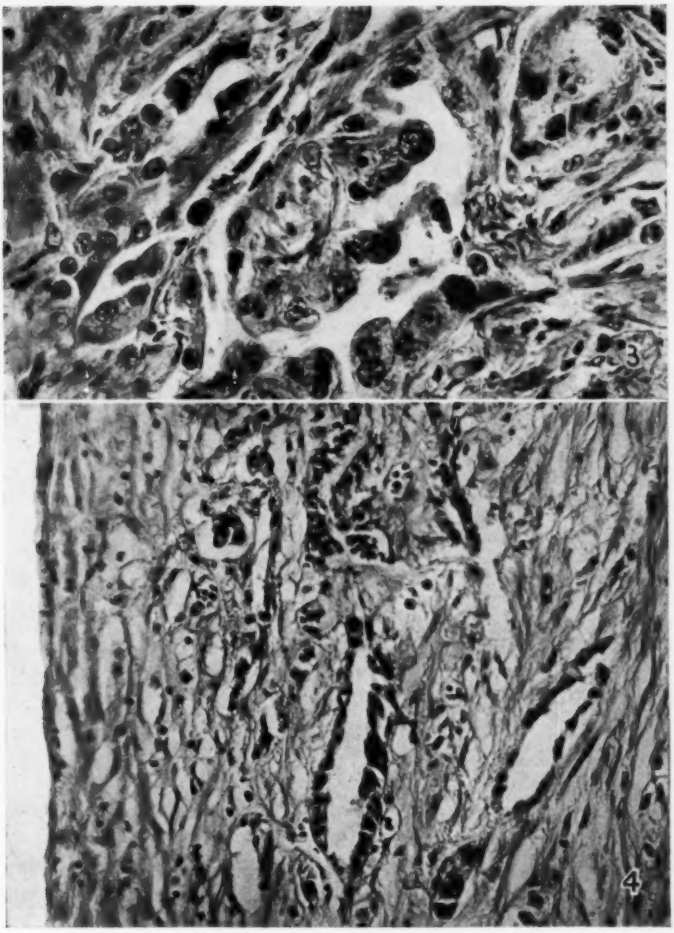

Fig. 3 (case 1).—Glands formed by a tumor nodule of the lower lobe of the right lung; × 690. They are lined with atypical cells; abnormal nuclei and mitoses are evident.

Fig. 4 (case 1).—Neoplasm invading visceral pleura of the lower lobe of the right lung; × 500.

Autopsy (Dr. F. A. Svec) revealed: primary alveolar cell carcinoma of the lungs with invasion of pleura and intrapulmonary lymphatics and metastases in mediastinal and cervical lymph nodes and the left adrenal gland; recent organizing thrombosis of peripheral branches of the pulmonary artery to the upper and lower lobes of the left lung; organizing infarcts in the upper and lower lobes

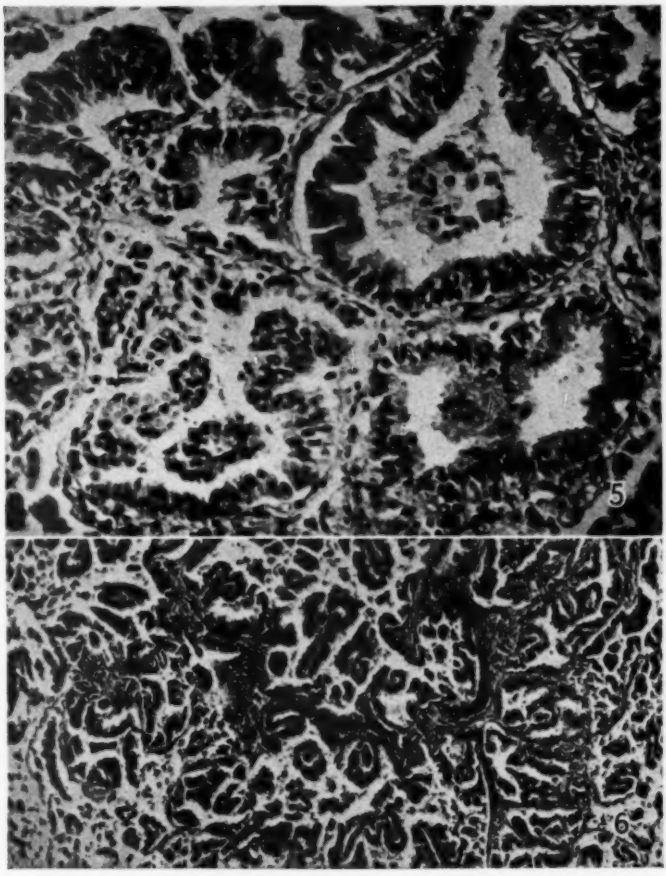

Fig. 5 (case 2).—Alveoli of the lower lobe of the left lung; × 500. Columnar cells without marked pleomorphism line the alveoli.

Fig. 6 (case 2).—Alveoli of the upper lobe of the right lung; × 65. They are lined with high columnar cells. Papillae of tumor project into alveolar spaces.

of the left lung; hydropericardium (500 cc.); hydrothorax of the left side (1,500 cc.); hypertrophy and dilatation of the heart, particularly of the right

atrium and the right ventricle (400 Gm.); marked passive hyperemia of viscera; slight arterial and arteriolar nephrosclerosis.

The right and left lungs weighed 1,150 and 900 Gm., respectively. The increase in size and weight was due principally to the presence of numerous nodules, varying from 0.1 to 1.5 cm. in maximum measurement. All the nodules were firm, pale yellow and sharply circumscribed from adjacent pulmonary tissue. They were diffusely distributed throughout all lobes of both lungs. None of the tumor nodules was outstanding in size, and bronchial involvement could not be demonstrated. Two pyramid-shaped, yellowish red infarcts were present in the left lung. The maximum measurement of the infarct in the upper lobe was 6 cm. and of that in the lower lobe 7 cm. The branches of the left pulmonary artery that supplied these regions were filled with adherent, firm, friable, reddish yellow thrombi. Microscopic examination of many sections from all lobes of the lungs showed the nodules to be similar at all sites. They were made up of richly cellular tumor of epithelial and papilliferous type (fig. 5). In many regions alveoli were lined with columnar tumor cells, which in most regions were of fairly regular type without definite variation in their size and staining properties. Papillae were evident in many regions (fig. 6), and sections stained by the mucicarmine method revealed mucin within tumor cells and within alveolar spaces that were lined with such cells. A complete autopsy was performed and no other site of primary tumor was demonstrated. The tumor is considered to be the multiple nodular type of primary alveolar cell carcinoma.

The heart, which weighed 400 Gm., showed significant enlargement of the right atrium and the right ventricle. The hypertrophy and the dilatation of these cardiac chambers are considered to be secondary to increased resistance to blood flow and probably increased pressure within the pulmonary circulatory system which resulted from compression and obliteration of pulmonary vessels. The thrombi in branches of pulmonary arteries and the infarcts in the left lung could have been contributing factors in reducing the volume of the pulmonary circulatory system. The immediate cause of death is considered to have been cardiac failure.

COMMENT

The clinical signs and symptoms of primary alveolar cell tumors are usually not diagnostic. The symptoms include cough, hemoptysis, cyanosis, dyspnea, pain in the chest and evidence of pleural effusion. Lack of fever, loss of weight, progressive weakness, a chronic course and obvious dyspnea are sometimes suggestive of a pulmonary tumor. Nevertheless, the roentgen changes are not pathognomonic. In the majority of the reported cases the condition has been diagnosed as either pneumonia (occasionally of atypical type) or tuberculosis.

In case 1 the patient had signs and symptoms that led to a diagnosis of Ayerza's disease. Changes noted at autopsy, i. e., diffuse fibrosis of the lungs, marked sclerosis of pulmonary arteries and arterioles, hypertrophy and dilatation of the heart, are consistent with such a diagnosis. According to Brenner's [26] classification, this would be secondary pulmonary arteriosclerosis, which is the type that evidently existed in the patient described by Ayerza in 1901. The gross and

26. Brenner, O.: Arch. Int. Med. **56**:211, 1935.

microscopic features of the lungs are like those of the diffuse type of pulmonary alveolar cell adenomatosis. The case differs from most recorded cases of this condition in that some of the cells lining alveoli had distinct cilia and in that there were foci of cancerous change. The two foci of invasive neoplasm in one lobe of the lung are considered to have originated from altered alveolar cells like those present in other parts of the lungs. It is thought, therefore, that this is an example of diffuse pulmonary alveolar cell adenomatosis with two foci of cancerous change. The case is classified as one of alveolar cell carcinoma.

It is worthy of note that a similar case was reported by Dacie and Hoyle.[5p] Diffuse pulmonary changes, one focus of "malignant" change and hypertrophy and dilatation of the right atrium and ventricle of the heart were noted. Another case in which focal cancerous change occurred was reported by Wood.[5q] These 2 cases, as well as our case 1, indicate that pulmonary alveolar cell adenomatosis may undergo cancerous change and support the view that pulmonary alveolar cell adenomatosis and alveolar cell carcinoma are related.

Our second case is one of the multiple nodular type of alveolar cell carcinoma. The cytologic aspect does not in itself clearly indicate that the lesion is cancerous. Nevertheless, the invasion of visceral pleura and of intrapulmonary lymphatics and the metastases in regional lymph nodes and in the left adrenal gland establish the cancerous nature of the tumor. In all probability there was partial obstruction and obliteration of many pulmonary vessels which led to increased resistance to blood flow and increased pressure within the pulmonary circulatory system. This in turn is considered to have caused the hypertrophy and dilatation of the right ventricle and ultimate cardiac failure.

SUMMARY

Two cases of pulmonary alveolar cell tumor of the lung are reported. One is considered to be a case of diffuse alveolar cell adenomatosis with two foci of cancerous change; the second is illustrative of bilateral multiple nodular alveolar cell carcinoma. In both instances the clinical signs and symptoms were those of chronic pulmonary disease with failure of the right side of the heart.

A review of the literature disclosed 45 acceptable cases of primary alveolar cell tumor. In 30 it had been established that the tumor was "malignant," and in 15, that it was "benign."

The striking similarity of morphologic features suggests but does not establish that there is a relationship between alveolar cell tumors of man and similar lesions in sheep, mice, horses and guinea pigs.

ARSENICAL ENCEPHALOPATHY

Report of a Case

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ACUTE hemorrhagic necrosis of the central nervous system following arsenical therapy has been described in the literature under the following terms: "hemorrhagic encephalitis," "cerebral purpura," "toxic myelitis," "toxic myelopathy," "medullary perivascular necrosis," "pericapillary encephalorrhagia" and "serous apoplexy." The term "arsenical encephalopathy," suggested by several authors of recent papers on the subject, seems more appropriate.

Since 1903, when "hemorrhagic encephalitis" was first described by Rosenfeld,[1] many cases have been recorded in the clinical literature, but Globus and Ginsburg[2] in reviewing the literature up to 1933 were able to collect only 60 such cases in which the diagnosis was confirmed by necropsy. At least 23 additional cases have been recorded since that time, providing a total of 83 published cases.

REPORT OF CASE

A 34 year old white pharmacist had, in December 1946, a urethral discharge and a penile lesion shown by dark field examination to be syphilitic. He was given a course of 2,400,000 units of penicillin intramuscularly over seven and one-half days. On Jan. 13, 1947, 0.3 Gm. of neoarsphenamine was given intravenously without apparent untoward effects. One week later 0.45 Gm. of neoarsphenamine was given intravenously. Forty-eight hours later he called the hospital and stated that he was aching all over, felt he was getting the "flu" and requested a prescription of codeine. At 2 p.m. of the same day his employer sent him home from work because he was listless and looked ill. The next morning the employer went to the patient's apartment and was unable to arouse him. A private physician found the patient disoriented, mentally confused and weak, with poor muscular coordination.

He was admitted to an out of town hospital, where examination revealed hyperactive reflexes, a bilateral Babinski sign, more marked on the right, and

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1. Rosenfeld, M.: Deutsche Ztschr. f. Nervenh. **24**:415, 1903.

2. Globus, J. H., and Ginsburg, S. W.: Arch. Neurol. & Psychiat. **30**:1226, 1933.

marked tonic contraction of the right leg. Papilledema was present bilaterally. The cerebrospinal fluid contained 6 leukocytes per cubic millimeter and gave a negative reaction in the Pandy test; the pressure was 400 mm. of water. The blood leukocyte count was normal. There was albuminuria (reaction for albumin, 1 plus). The temperature was normal and the pulse rate 60 per minute. The patient remained unresponsive and soon became incontinent of urine.

He was admitted to the Veterans Administration Hospital, January 25, seventy-two hours after onset, with a diagnosis of brain tumor. At this time he was entirely unresponsive even to painful stimuli. The body temperature was 102.2 F. (rectal); pulse rate, 150; blood pressure, 120 systolic and 100 diastolic; respiratory rate, 40. The pupils were dilated and fixed, and the eyes appeared to drift to the left. Funduscopic findings were normal. There was a mucopurulent nasal discharge. Respirations were rapid and stertorous. Breath sounds were reduced at the bases of both lungs, and fine crepitant rales were heard over the left lateral chest wall. All extremities were flaccid. Tendon reflexes appeared normal in the upper extremities but were absent in the lower. Hoffmann's sign was not present. Babinski, Oppenheim, Chaddock and Gordon signs were present bilaterally.

On admission lumbar puncture revealed a pressure of 140 mm. of water. The fluid contained 6 leukocytes per cubic millimeter; the protein content was 190 mg. per hundred cubic centimeters, and serologic tests for syphilis (Kolmer and Kahn) were negative. The colloidal gold curve was 0112332000. Cultures were negative. The urine contained albumin (3 plus), 4 leukocytes and 10 to 15 erythrocytes per high power field, and was loaded with finely granular and hyaline casts. The blood leukocyte count was 12,700, with 86 per cent mature neutrophils, 12 per cent lymphocytes and 2 per cent monocytes. Blood urea nitrogen was 31 mg. and blood sugar 102 mg. per hundred cubic centimeters, and the blood serum Kahn and Kolmer tests were negative.

Urine and blood showed no significant alteration of the findings mentioned on repeated examination. A progressive drop in the spinal fluid protein with a significant rise in pressure was noted.

Temperature and pulse rate continued to rise, the temperature reaching a high of 107 F. Tendon reflexes disappeared, first on the left and a day later on the right. Penicillin was given intramuscularly, 30,000 units every four hours, and general supportive measures were initiated. On the third day of hospitalization a diagnosis of arsenical encephalopathy was made, and treatment with 2, 3-dimercaptopropanol (British anti-lewisite, or BAL) was begun, 7 cc. every four hours, and continued until death. An electrocardiogram indicated myocardial damage. Death occurred at 3:45 a.m. on the fourth day, sixty-eight hours after admission, one hundred and forty hours after onset and one hundred and eighty-eight hours after the last injection of neoarsphenamine.

Postmortem Observations.—There were bilateral confluent bronchopneumonia, mucosal hemorrhages of the stomach and the urinary bladder and slight capsular hemorrhage of the right adrenal gland. The large arteries showed moderate atheromatosis.

The weight of the fresh brain was 1,565 Gm. The gyri of both hemispheres showed slight flattening. Examination of frontal sections of the brain followed fixation in 4 per cent formaldehyde solution. At the level of the optic chiasm there were punctate hemorrhages in the white substance beneath the island of Reil, occurring in symmetric areas. A few scattered small hemorrhages were seen in the white substance of the frontal lobes.

In a section immediately anterior to the mamillary bodies there were hemorrhages in bilateral symmetric areas in the white substance beneath the island of Reil and bordering on the putamen. On the right side the center of the hemorrhagic area appeared necrotic. An area of closely spaced petechial hemorrhages was found on the left side of the corpus callosum. Isolated hemorrhages were seen throughout the white substance and extremely fine petechiae could be seen in the gray cortex of the right parietal lobe.

In a section immediately posterior to the mamillary bodies, symmetric areas of hemorrhagic necrosis were found on each side of the corpus callosum. Petechial hemorrhages were present in the ependyma of the inferior cornu of each lateral ventricle.

In a section through the nucleus ruber, symmetric hemorrhages and necrosis of the corpus callosum were seen similar to those found in the previous section. Small clumps of petechial hemorrhages were found in the lateral portion of each thalamus, and those on the right were the more prominent.

In a section through the pineal gland, symmetric hemorrhages of the corpus callosum and of the walls of the inferior cornu of each lateral ventricle were evident.

In a section through the posterior extremities of the lateral ventricles, an uneven zone of hemorrhage up to 1.0 cm. in width surrounded each lateral ventricle, and that on the right was slightly more prominent.

As to the brain stem and cerebellum, transverse sections through the upper one third of the pons showed bilateral symmetric hemorrhagic necrosis of the anterior two thirds (fig. 1). Necrosis and hemorrhage extended throughout the pons to its junction with the medulla oblongata, but not caudal to this. The medulla and the entire spinal cord showed dilated veins on the surface of the cord and a few perivascular hemorrhages in the medullary substance.

Microscopic Examination of Brain.—Paraffin sections were stained by hematoxylin and eosin, Mallory phosphotungstic acid–hematoxylin and Van Gieson methods.

Medial Portion of Occipital Cortex, Including Lateral Ventricle: The principal lesions were in the white substance around the wall of the lateral ventricle and consisted of advanced degeneration and poorly defined areas of necrosis in a broad irregular zone around the ventricle. All of the necrotic foci were surrounded by broad areas of interstitial hemorrhage. Most of the small vessels, including arterioles, capillaries and venules, were occluded by thrombi. The walls of many of the arterioles and capillaries appeared necrotic, but leukocytic infiltration was minimal. There was no appreciable degree of proliferation of the glia. Areas of degenerated brain substance around and between the hemorrhages were coarsely vacuolated. Evidence of degeneration of the cortical gray substance was slight. Perivascular edema was slight.

Claustrum: The lesions consisted of a poorly defined area of necrosis and innumerable sharply defined perivascular hemorrhages in a broad zone around the area of necrosis (fig. 2). One or more necrotic small blood vessels were found within each circle of hemorrhage. Almost all of the arterioles, venules and capillaries appeared to be occluded by fibrinous thrombi, which appeared deep purple to black in the sections stained with phosphotungstic acid–hematoxylin. The erythrocytes were preserved. Small numbers of polymorphonuclear neutrophils infiltrated the necrotic tissue. The cortical gray substance was involved only to a slight degree, the abnormalities consisting of a few widely spaced perivascular hemorrhages and thrombosed small blood vessels.

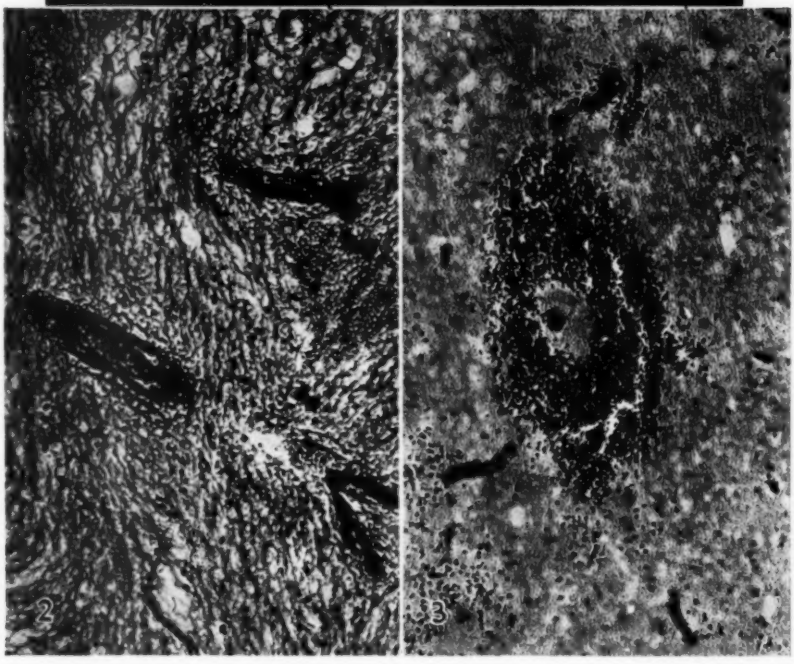

Fig. 1.—Bilateral hemorrhagic necrosis of the pons.

Fig. 2.—Section from area of claustrum, showing arteriolar necrosis, perivascular hemorrhage and thrombosis of capillary blood vessels. Mallory's phosphotungstic acid–hematoxylin; × 77.

Fig. 3.—Section of corpus callosum. Note necrosis and thrombosis of small blood vessels and vacuolation associated with demyelination. Mallory's phosphotungstic acid–hematoxylin; × 385.

Corpus Callosum and Adjacent Cortex: The lesions were most advanced in the white substance and involved particularly the lateral portions of the corpus callosum. On each side there was an irregular area of necrosis within which all of the small blood vessels were occluded by thrombi. The necrotic tissue was fenestrated and lightly infiltrated by neutrophils and a few lymphocytes. In broad zones surrounding the necrotic areas and in the white substance of the central portion of the corpus callosum there were numerous areas of perivascular hemorrhage which varied greatly in size (fig. 3). The ependymal cells lining the ventricles and covering the choroid plexus showed no definite pathologic alteration. The small areas of gray cortex were essentially normal. The interstices of the arachnoidal membrane were infiltrated by well preserved erythrocytes.

Rostral Portion of the Pons: In the dorsal one third there were no lesions except irregularly scattered small perivascular hemorrhages involving both the nuclear masses of the middle portion of the pons and the brachium conjunctivum. In the ventral two thirds these hemorrhages were both more numerous and larger and tended to surround two large areas of necrosis, one on each side of the midline. The latter areas were irregular, about equally extensive on the two sides but not exactly symmetric. Near the center of the hemorrhagic patches, small thrombosed blood vessels were surrounded by zones of necrosis. The walls of some of the larger vessels appeared to be necrotic, and these were infiltrated by neutrophils. Similar leukocytic infiltrates surrounded some of the occluded hyalinized arterioles and capillaries. Many thrombosed blood vessels lay in the seminecrotic tissue which surround the larger necrotic areas. Evidence of glial proliferation was slight.

Pons, Middle One Third, Including Root of Trigeminal Nerve: The ventral three fourths of the pons was involved in a process similar to that described in the previous level. On one side an almost round area of necrosis extended from the ventral surface dorsally and crossed the median line. A second area, quite irregular in outline, was located on the opposite side and extended from the ventral surface dorsally to the junction of the middle and dorsal thirds. The small cavities formed in these areas were largely occupied by necrotic tissue and blood. Many small blood vessels showed necrosis and infiltrating neutrophilic leukocytes and were surrounded by broad irregular zones of hemorrhage. The degenerated tissue which formed the walls of the cavities was coarsely vacuolated. In the dorsal one fourth a few of the larger blood vessels were occluded by thrombi and surrounded by zones of necrosis of brain tissue with loss of substance. No gliosis was evident in this section.

Medulla, Upper Level: Two small areas of perivascular hemorrhage were located just beneath the floor of the fourth ventricle, one on each side. The olivary nuclei were not seriously involved, but the white substance of the hilus contained a few venules which were partly collapsed and surrounded by narrow zones of hemorrhage and edema. A small area of anemic necrosis with light interstitial hemorrhage lay just ventral to one of the olivary bodies.

Spinal Cord: It was essentially normal.

Hypophysis: No lesions were recognized.

Chemical Analysis.—The Gutzeit test revealed 0.6 mg. of arsenic per hundred grams of brain tissue.

Bacteriologic Examination.—The spinal fluid gave no growth.

COMMENT

According to Kinnier Wilson,[3] 50 per cent of deaths caused by arsenicals in all countries have been due to "hemorrhagic encephalitis." Ingraham [4] reported 7 deaths due to arsenic, 1 from encephalopathy that was demonstrated at autopsy. However, in his review of 35 fatal arsenical reactions, 27, or 64 per cent, of the patients were said to have died from arsenical encephalopathy. Burton and associates [5] reported 18 deaths due to arsenic, 3 of which resulted from cerebral complications. Woods [6] reported 12 fatal poisonings, 6 of which had resulted in "hemorrhagic encephalitis." Stokes [7] observed 1 arsenical reaction in 63,000 injections; Glaser and associates [8] in a review found 1 death due to encephalopathy in every 5,398 patients treated and 1 in every 28,768 injections. It has been suggested that the cerebral lesions occur much more frequently than statistics indicate.[9]

Males are more often affected. Of the 17 females whose cases have been reported, 8 were pregnant. Pregnant women are more subject to the disastrous as well as to the beneficial effects of antisyphilitic therapy than are other persons. Cole's [10] statistics indicate that patients with latent syphilis are more prone to reactions than those with early lesions, and a latent infection is the common finding in pregnant women.

Not all arsenical encephalopathy is found in syphilitic patients. Several reports have appeared with records of typical clinical and pathologic observations in cases in which the patients were treated with arsenicals for other diseases. Glaser and associates [8] reported encephalopathy in a case of multiple sclerosis in which an organic arsenical was given. Burton and co-workers [5] and Smith and Newbill [11] reported cases of Vincent's infection in which the patients were treated with arsenic, and Waraich and associates [12] described a case in which a patient

3. Wilson, K. S. A.: Neurology, London, Edward Arnold & Co., 1940.

4. Ingraham, N. R.: J. A. M. A. **112**:1537, 1939.

5. Burton, O. L.; Justyn, G. W., and Anderson, L. T.: U. S. Nav. M. Bull. **46**:139, 1946.

6. Woods, E. B.: J. M. A. Georgia **25**:23, 1946.

7. Stokes, J. H.: Modern Clinical Syphilology, ed. 2, Philadelphia, W. B. Saunders Company, 1934.

8. Glaser, M. A.; Imerman, C. P., and Imerman, S. W.: Am. J. M. Sc. **189**: 64, 1935.

9. Nelson, R. B.; McGibbon, C., and Glyn Hughes, F.: Brit. M. J. **1**:661, 1943.

10. Cole, H. N.: J. A. M. A. **97**:897, 1931.

11. Smith, D. C., and Newbill, H. P.: South. M. J. **32**:381, 1939.

12. Waraich, G. S.; Stone, L., and Kessler, M. M.: Bull. Meninger Clin. **1**:385, 1936.

treated for acute cystitis died of "arsenical encephalopathy" following the administration of arsenic. Ecker and Kernohan [13] described the pathologic observations in 12 cases in which the patients died with symptoms of diffuse cerebral damage. None of them had syphilis, and none was known to have received organic or inorganic arsenic, yet chemical assay of the brains revealed 0.1 to 0.83 mg. of arsenic per hundred milligrams of tissue. (The concentrations were similar to those found in cases of arsenical encephalopathy.) They studied also 12 cases of hypertensive vascular disease with signs, symptoms and duration similar to those of the first group, and in none of the brains was an appreciable amount of arsenic found. It was concluded that these 12 cases of "subacute encephalomyelitis" represented instances of "chronic arsenical poisoning." The source of the arsenic was assumed to be food, water, etc. No theory as to why hypersensitivity developed in these particular persons was offered. A similar study with similar results was carried out by Otserberg and co-workers,[14] who concluded that in cases in which the clinical picture is one of "hemorrhagic encephalitis" arsenic should be considered as the etiologic agent.

Signs and symptoms of the disease usually appear about forty-eight hours after the second or third injection of the first course of injections of an organic arsenical. Headache, confusion and irritability are the first and most common symptoms, followed by nausea and vomiting, progressive stupor, convulsions, hyperpyrexia and death. Signs of injury of the central nervous system are, in order of their frequency: changes in deep tendon reflexes, loss of corneal reflex, disturbance of speech, tremors, loss of light reflex, hemiplegia, nystagmus and facial palsy. Meningismus is rare. In patients who recover, bizarre neurologic findings and transient mental aberrations are seen.

The blood picture is usually within normal limits if infection has not intervened. The urine may show albumin (1 to 3 plus), but the degree of albuminuria is not correlated with the degree of damage of the central nervous system. Microscopic hematuria is often seen, as would be expected in cases of generalized increase of capillary permeability. Cerebrospinal fluid pressure is initially normal, but later, as cerebral edema occurs, the pressure tends to rise. The spinal fluid protein is elevated in cases of the most severe types.

13. Ecker, A. D., and Kernohan, J. W.: Arch. Neurol. & Psychiat. **45**:24, 1941.

14. Osterberg, A. E.; Brunsting, L. A., and Montgomery, H.: Proc. Staff Meet., Mayo Clin. **10**:152, 1935.

The mortality rate is high, approximately 75 per cent of recognized cases terminating in death, which occurs usually within five to seven days after the last injection of arsenic. However, several recoveries have been reported.[15]

Pathologically, the majority of the patients whose cases have been reported have shown similar changes in varying degrees. Cormia[16] stated, "The different syndromes are expressions of varying degrees of severity of the same essential process."

The lesions show a predilection for the white substance of the brain, with only mild congestion in the gray matter. The classic description by Kinnier Wilson[3] leaves little to be added:

> Hemorrhagic encephalitis is distinguished by abundant small perivascular effusions, mostly of the ring type; plugged capillaries with minute necrotic zones around them and sometimes incomplete partial occlusion in larger vessels; on occasions these thrombi are hyaline. Interstitial reactions otherwise (cellular infiltration of vessel coats rather than of perivascular spaces) are never pronounced and frequently lacking.
>
> Subpial extravasation may be present in the optic thalami, cornu ammonis, tegmentum, pons and elsewhere. At times, however, nothing more than congestion and edema is discovered. Moderate demyelination around hemorrhagic zones is also seen occasionally.

The process probably begins with congestion and edema, followed by thrombosis, hemorrhage, demyelination, gliosis and ultimately necrosis of the vessel wall and surrounding brain substance, with occasional progression to cyst formation. The pericapillary hemorrhages or "ring hemorrhages" often coalesce to form large bilaterally symmetric areas of hemorrhage. Certain areas are more susceptible than others, i. e., the corpus callosum, the caudate and lenticular nuclei, the pons and the medulla. However, hemorrhage has been reported to involve almost all of the brain substance. The bilateral symmetry of these lesions is a striking feature which has been commented on by many authors.

Almost identical gross and microscopic changes have been observed in many other conditions, including poisoning due to carbon monoxide and phosgene gas, tuberculosis meningitis, meningitis due to other bacteria, influenza, pneumococcic pneumonia, malaria, typhus, pernicious anemia, secondary anemia, erythema multiforme, psoriasis, scurvy, cere-

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15. Thomas, E. W.; Wexler, G., and Dattner, B.: Am. J. Syph., Gonor. & Ven. Dis. **26**:529, 1942. Lees, D.: Practical Methods in the Diagnosis and Treatment of Venereal Disease, ed. 3, London, Butterworth & Co., 1937. Netherton, E. W.: M. Clin. North America **17**:1005, 1934. Dickens, P. F.: U. S. Nav. M. Bull. **26**:192, 1928. Parnell, R. J. G., and Dudley, S. F.: Lancet **1**:190, 1920. Gjessing, H. C.: Acta dermat.-venereol. **8**:268, 1927.

16. Cormia, F. E.: Canad. M. A. J. **35**:610, 1936.

bral thrombosis, cerebral trauma, and meningovascular syphilis, and they may be secondary to cerebral circulatory disturbances caused by hemorrhage, thrombosis or tumor.

Pathogenesis.—There is such an array of findings associated with arsenical encephalopathy that it is not surprising that no one theory yet proposed has proved entirely satisfactory. There have been many suggestions as to the genesis of this process, and one of the first and one which received much support in the early days was proposed by Ehrlich.[17] He was of the opinion that the damage of the central nervous system was not due to the direct effect of the drug, and he insisted that yellow atrophy of the liver alone should be considered as a direct effect of the drug intoxication. He maintained that the cerebral injury is an expression of a Herxheimer reaction. This theory, however, has since been disproved, since numerous cases of arsenical encephalopathy have been observed in persons who did not have syphilis.[18]

Pathologic evidence of arsenical encephalopathy occurring in the presence of acute encephalitis and parenchymatous cerebral syphilis has been described. However, the question of death due to a Herxheimer reaction must be raised.[4]

Brown and Pearce [19] found that in animals given toxic doses of arsenic marked congestion, hemorrhage and necrosis of the adrenal glands developed. On the basis of the results of this study it has been suggested [20] that the vascular damage is the result of an insufficiency of epinephrine, the substance assumed to be necessary to counteract the vasodilating effect of arsphenamine. Epinephrine has been widely used in the treatment of this condition, almost always without avail.

Since symptoms occur most frequently after the second injection, it seems possible that the mechanism of the cerebral injury may be allergic in nature. Halcrow [21] suggested that disintegration products of arsenic preparations have a toxic action on the capillaries. Thrombopenic purpura is a well known result of organic arsenical toxicity, and it is possible that the encephalopathy is due to disintegration of arsenobenzine compounds in the blood with resulting thrombopenia and capillary damage.

Friedman and Newman [22] reported 2 cases of arsenical encephalopathy in which the patients were infants, 6 and 14 months of age. They offered the theory that there is a delay of metabolism of the arsenic due

17. Cited by Scheinker, I. M.: Arch. Path. **37**:91, 1944.

18. Pritzi, O.: Zentralbl. f. Gynäk. **52**:2930, 1928. Glaser and others.[8] Smith and Newbill.[11] Waraich and others.[12]

19. Brown, W. H., and Pearce, L.: J. Exper. Med. **22**:535, 1915.

20. Vail, A. D.: J. Missouri M. A. **38**:110, 1941. Cormia.[16]

21. Halcrow, J. P. A.: Brit. M. J. **1**:663, 1943.

22. Friedman, E. D., and Newman, E.: J. Nerv. & Ment. Dis. **94**:606, 1941.

to hepatic insufficiency and accumulation in the body of toxic products of the drug because of renal dysfunction. Thus hypersensitivity to arsenic or its metabolites develops, and the patient dies an anaphylactoid death when another injection is given.

Others [17] have expressed the belief that the vascular lesions occur as a result of an acute physical or chemical irritation, and after vasoconstriction of short duration there soon occurs a paralytic dilatation of the affected vessel, usually associated with stasis. If the circulation is impaired because of this process, a local accumulation of carbon dioxide occurs and interferes with the oxygen supply to the capillaries. If these alterations become severe, degeneration of the vessel wall occurs, with increased permeability to serous fluid and red blood cells. Extravasation occurs and results in further stasis due to pressure and tissue starvation. Thus a vicious cycle is set up which eventually may result in degeneration and necrosis of the surrounding tissue.

Out of the confusion which exists concerning the genesis of arsenical encephalopathy, we may conclude that the mechanism is vascular in nature and that the pathologic changes, in most cases, are out of proportion to the apparent functional damage of the central nervous system.

SUMMARY

A patient was treated for early syphilis with penicillin, followed by neoarsphenamine, which was administered in two intravenous injections. Death occurred eight days after the last injection. Treatment with 2, 3-dimercaptopropanol (BAL) was begun on the fifth day after the onset of cerebral symptoms (seven days after the last injection of neoarsphenamine) without apparent effect.

The cerebral lesions consisted of thrombosis of arterioles and capillary blood vessels, necrosis of arterioles, perivascular hemorrhages and hemorrhagic necrosis of brain substance. There was marked symmetry of the lesions, and the white matter was principally affected, especially the pons, the corpus callosum, the claustrum and the thalamus. An unusually high level of arsenic was found on chemical analysis of the brain.

The pathogenesis and the gross and microscopic lesions are discussed, and the available literature since 1933 is reviewed.

EFFECT OF EXPERIMENTAL THIAMINE DEFICIENCY ON THE NERVOUS SYSTEM OF THE RHESUS MONKEY

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DURING the course of studies of rhesus monkeys which had been subjected to one or more episodes of thiamine deficiency we observed, repeatedly, widespread degenerative lesions of gray matter, differing somewhat in distribution, extent and histopathologic nature from the Wernicke type of lesion. These observations have been reported in abstracts.[1] Because in distribution these lesions resembled those encountered in certain diseases of the human central nervous system and varied from what is usually reported in thiamine deficiency, and because there was an absence of peripheral neuropathy in these animals, the findings are reported in detail and are compared with those previously reported observed in man and animals.

The diet, the laboratory findings and the response of the animals to deficiency episodes and thiamine supplements have been described separately,[2] as have the characteristic lesions of the heart.[3]

TECHNIC OF EXAMINATION

The formaldehyde-fixed brains of 7 monkeys were sliced coronally, and sections were taken at about 3 mm. intervals throughout the basal ganglions and brain stem, as well as representative areas of cortex, and embedded for histologic study. The spinal cord was sectioned at segmental intervals and all sections examined except in the case of the first 3 monkeys, from which only random sections were taken. Sections of cord and of the sciatic nerve and some of its larger branches were fixed in Müller's fluid for osmic acid stains. The usual stains were employed with Laidlaw's connective tissue stain as a satisfactory substitute for the benzidine stain for capillaries.

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This investigation was aided by a grant from the California Fruit Growers Exchange and the A. B. Miller Fund.

1. Rinehart, J. F.; Friedman, M., and Greenberg, L. D.: Tr. Am. Neurol. A. **72**:174, 1946. Rinehart, J. F.; Greenberg, L. D., and Friedman, M.: Am. J. Path. **23**:879, 1943.

2. Rinehart, J. F.; Greenberg, L. D., and Ginzton, L. L.: Blood **3**:1453, 1948.

3. Rinehart, J. F., and Greenberg, L. D.: Arch. Path. **48**:89, 1949.

PATHOLOGIC OBSERVATIONS

Gross Findings.—There were areas of softening in the corpus striatum (chiefly the putamen) in 4 monkeys. In 3 animals these confluent small rounded areas of 3 to 8 mm. size had sharply defined borders, with the softened part tending to shrink away from the normal tissue. In the fourth the borders were poorly defined, and the softened areas

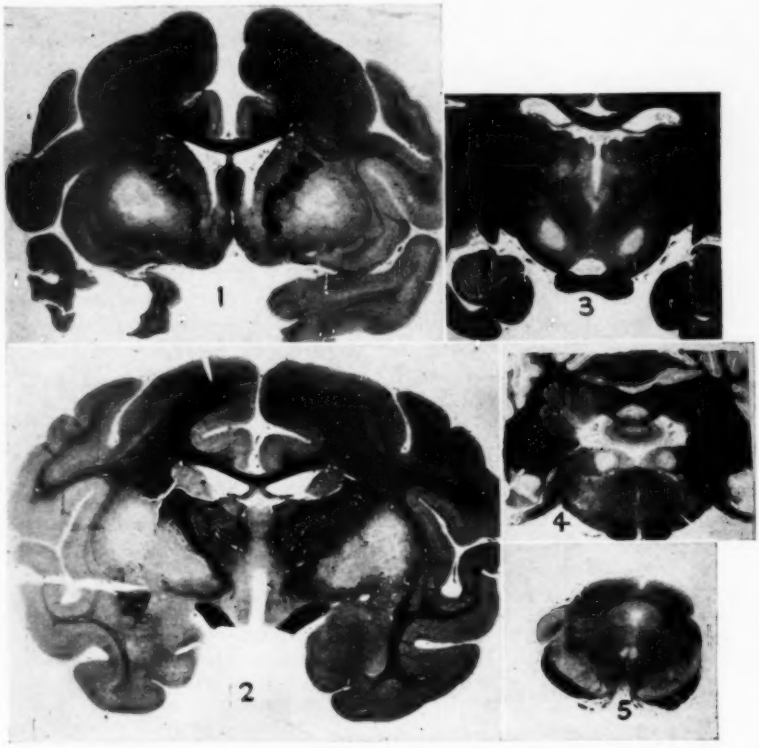

Fig. 1.—Symmetric degeneration of putamen; Weil stain; × 1.5.
Fig. 2.—Symmetric degenerations of lenticular nucleus; Weil stain; × 1.7.
Fig. 3.—Symmetric degenerations in subtantia nigra and small lesions in median portion of thalamus; Weil stain; × 1.5.
Fig. 4.—Symmetric degeneration of nuclei of eighth cranial nerves; Weil stain; × 2.
Fig. 5.—Symmetric degenerations of nuclei of third cranial nerve; Weil stain; × 2.

had a very pale yellowish coloration and one or two concentric narrow pale rings. In 1 animal there were a few small areas of softening and pallor in the cortex of the left frontal lobe near the central fissure.

In the spinal cords, tiny reddish brown spots were seen occasionally in the gray matter.

Histologic Observations.—1. The earliest changes appeared to be localized edema of tissue, with fluid separating glial and nerve fibers, and fragmentation and disintegration of the myelin sheaths in this area. A few microglial cells were seen within such areas, and at the borders of the areas there were sparsely formed rings of these cells in various stages of transformation from the quiescent to the phagocytic form. The nerve cells were usually normal at this stage, which is designated as "early" in table 1.

2. A severe lesion of apparently rapid development was seen sometimes in the putamen and the substantia nigra and consisted of slight edema, demyelination, loss of staining qualities in all tissue elements and necrosis and liquefaction of most nerve cells. The nerve cells still present in these areas had acidophilic, granular cytoplasm and pale, weakly acidophilic nuclei. A scanty margin of microglial cells and a few astrocytes were seen at the borders of such areas. This change was not unlike an anemic infarct and is designated as "early severe" in table 1.

3. With further progression of either type of change there were found disintegration of axis-cylinders, degeneration of glia and progressive accumulation of many microglial cells and a few astrocytes. Usually several of the nerve cells (but sometimes surprisingly few) had undergone acute swelling or severe cell disease with disintegration (figs. 6 and 9). This stage is designated as "moderately advanced, focal" in table 1. None of the animals was maintained sufficiently long after reaching the deficient stage to carry the changes to the point where scars or extensive gliosis occurred.

4. Around, and particularly between, some of the older lesions in the corpus striatum there was a diffuse, poorly demarcated area of changes consisting of degeneration of some nerve cells and some fibers and marked proliferation of astrocytes, many of which were beginning to assume the gemästete appearance.

Vascular changes conforming somewhat to those seen in the Wernicke type of lesion, but without petechiae, and consisting of dilated, tortuous capillaries with some endothelial proliferation and sometimes actual new vessel formation were occasionally seen (fig. 7). They occurred only in the oldest, severest lesions in those animals which were on the most prolonged deficiency regimen. They were noted chiefly in the putamen and never in the corpora mamillaria or the thalamus, and they appeared to be an attempt at repair of injured tissue rather than a primary lesion. The Laidlaw connective tissue

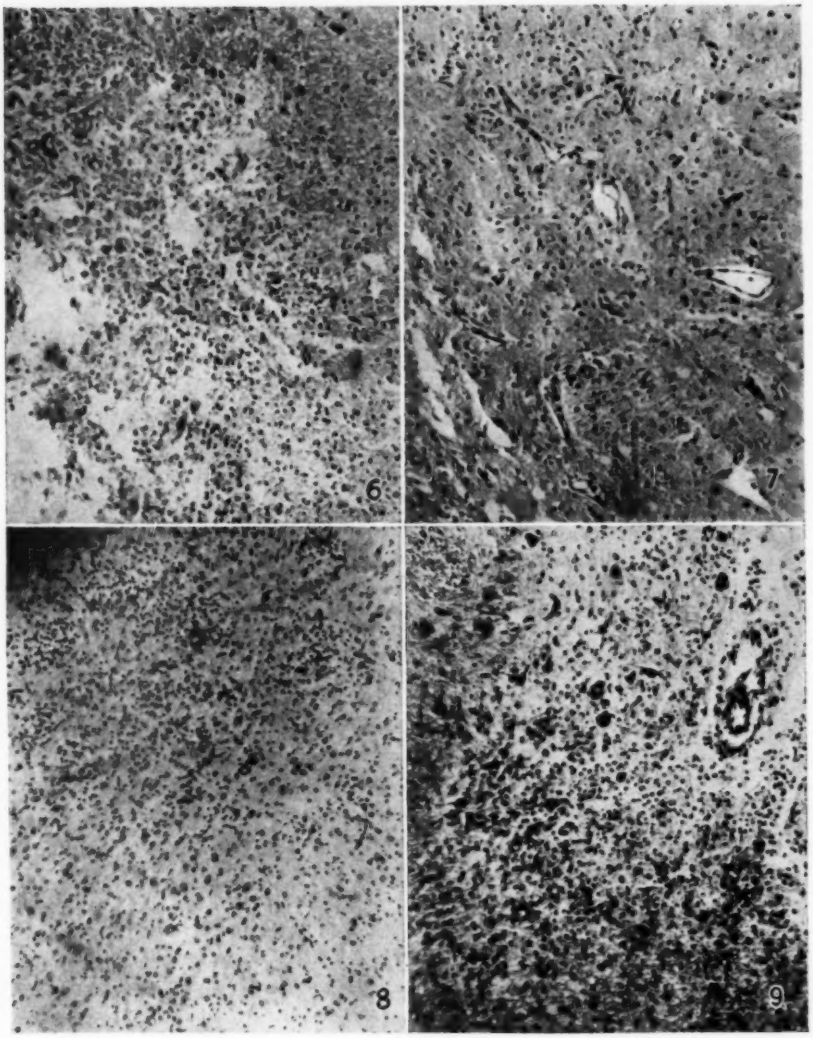

Fig. 6.—Inflammatory and scavenger cells at edge of region showing advanced stage of degeneration in putamen; hemalum-eosin stain; × 80.

Fig. 7.—Vascular dilatation and proliferation and inflammatory and scavenger cells near edge of older lesion in putamen; hemalum-eosin stain; × 80.

Fig. 8.—Inflammatory cells in degenerating portion of inferior colliculus of corpora quadrigemina; hemalum-eosin stain; × 80.

Fig. 9.—Inflammatory cells and degenerating neurons in nucleus of third cranial nerve; hemalum-eosin stain; × 125.

stain and even the hematoxylin-eosin stain proved generally satisfactory for studying the vascular changes.

In the spinal cord there were some petechiae, usually in the gray commissure, in about half of the animals.

In the peripheral nerves (and in random distribution in the spinal cord) there were a few scattered black particles in Marchi-stained sections, sometimes in myelin sheaths and sometimes outside. Axis-cylinders were normal; myelin sheaths appeared normal in hematoxylin-eosin, fat, myelin and other stains; no inflammatory cells or

TABLE 1.—*Lesions in 7 Monkeys*

	Animals			
	Number	Percentage	Type of Lesions	Degeneration of Nerve Cells
Caudate nucleus	4	57	Early severe, advanced focal and advanced diffuse	Severe
Putamen	5	71	Same as above	Severe
Globus pallidus	2	28	Early severe	Mild
Thalamus, median nucleus	2	28	Early severe, advanced focal	Moderate
Substantia nigra	1	14	Early severe	Moderately severe
Nucleus centralis superior	2	28	Advanced focal	Mild
Mamillary bodies	1	14	Moderately early focal	Mild
Inferior colliculi of tectum	4	57	Early and advanced focal	Mild to moderate
Nucleus fasciculus solitarius	2	28	Early	None
Cranial nerve III (oculomotor) nucleus	3	43	Advanced focal	Mild to moderate
Cranial nerve VI (abducens) nucleus	3	43	Advanced focal	Mild
Cranial nerve VIII (auditory) nucleus	2	28	Advanced focal	Moderate
Cranial nerve X (vagus) nucleus, dorsal	3	43	2 early, 1 Wernicke (no. 353)	Slight
Nucleus parvocellularis annuli aqueductus	1	14	Early	None
Cerebellar vermix	4	57	Moderately advanced focal	Mild
Cerebral cortex	1	14	Early severe	Moderately severe
Spinal cord, gray substance	3 or more	..	Rare petechiae only	None

phagocytes were seen, and it was concluded that the black particles in the Marchi stain, unlike "Marchi balls" in appearance and distribution, were artefacts. The peripheral nerves were therefore considered normal. Myoneural junctions were studied in 1 case and were found to be histologically normal.

Distribution of the Lesions: These lesions were entirely restricted to the gray matter of the central nervous system, chiefly to the basal ganglions and the brain stem. They were almost always bilateral and usually so nearly symmetric and bilaterally equal as to be "mirror images" of each other. The largest, most consistently occurring and most striking lesions were in the corpus striatum (figs. 1 and 2),

where degeneration of nerve cells was also generally most extensive. The cerebral cortex was involved in only 1 animal, and small foci were found in the vermis of the cerebellum in 4. Table 1 summarizes the distribution of the lesions.

CORRELATION OF LESIONS WITH BEHAVIOR OF ANIMALS

The common result of deficiency in all animals was profound weakness; some had ataxia, and a few had focal signs. The correlation of the lesions with definite signs in some animals was as follows:

Lesions in:	*Signs*
Corpus striatum, cranial nerve VI (abducens) nucleus, cerebellar cortex	Ataxia
Inferior colliculus, nucleus fasciculus solitarius	Ataxia
Corpus striatum, cranial nerve X (vagus) nucleus, cerebellar cortex, cranial nerve VI nucleus	Localized tonic convulsion, tends to walk in circles
Corpus striatum, globus pallidus, thalamus, inferior colliculi, cranial nerve VIII (auditory) nucleus, subthalamic body	Ataxia, hypersensitivity to auditory stimuli
Corpus striatum, globus pallidus, thalamus, mamillary bodies, cranial nerve III (oculomotor), VI and X nuclei, cerebellar cortex	Ptosis
Corpus striatum, inferior colliculi, cranial nerve III nucleus, cerebellar cortex	Ptosis, ataxia

Although specific clinical findings were meager, they did agree fairly well with anatomic findings, for example, the ptosis in 2 animals with severe lesions of the oculomotor nuclei, and the hypersensitivity to sound of 1 animal with a lesion in the eighth cranial nerve nucleus. The small size of cerebellar cortical lesions seemed inadequate to explain the ataxia unless degeneration in one area of cortex may signify a widespread predegenerative paralysis of other cerebellar cortical cells.

COMMENT

Nature of Degenerative Process.—The lesions resemble, in most instances, anemic infarction or degeneration such as ordinarily follows subtotal occlusion or temporary spasm of an artery. The ischemic changes of the nerve cells, the degeneration of nerve fibers, the circumscribed nature of the lesion and the cellular reaction at the edges of the larger lesions all point toward this resemblance. However, neither thrombi nor other vascular occlusive process could be demonstrated histologically. Vasospasm could easily produce the observed changes, but use of this hypothesis would necessitate further explanations for the occurrence of bilateral, exactly symmetric lesions, the avoidance of white matter (which is commonly involved in such infarcts in man) and the relative resistance of nerve cells. A more acceptable,

although as yet unsupported, explantion might be based on a purely chemical change, such as accumulation of an excess of pyruvic acid or other metabolites.

Explanation of Localization.—The restriction of the observed lesions chiefly to the axial gray matter of the central nervous system has, as yet, no obvious explanation. Bender and Schilder,[4] in discussing encephalitis hemorrhagica as observed in alcoholism, stated their belief that the lesions were associated with the flow of cerebrospinal fluid and were most severe where there was stagnation of fluid. Subsequent observations, and particularly the finding of large areas of devastation in the putamen in most of our animals, refute this concept. The finding of lesions of the striatum and striopallidum and most particularly of the putamen itself emphasizes again the general susceptibility of that region to many diseases of known and unknown cause (Wilson's disease; Parkinson's disease; Huntington's chorea; kernicterous; manganese, carbon monoxide and carbon disulfide poisoning), as yet unexplained. Hiller's[5] theory of electivity of diseases may be of some help. In his opinion susceptibility of a tissue to disease is determined by the paucity of the blood supply or by a high rate of metabolism. He mentioned the relatively poor blood supply to the corpus striatum (due partly to the scanty vascular tree and partly to acute angulation of the vessels, which impedes the flow). We are tempted to carry his concept one step further and consider the susceptibility of tissue to be related to the ratio of metabolism to vascularity. This would explain in our present experiments the selectivity for the gray matter, which has greater vascularity but much greater metabolic activity than the white matter, and the relative sparing of the cerebral cortex, which may have a considerably better vascularity than the subcortical gray matter.

Relation to Wernicke's Encephalopathy.—The lesions of the central nervous system described in the foregoing pages correspond in a general way to the polioencephalitis hemorrhagica of Wernicke in human subjects and its equivalent in many experimental animals restricted to thiamine-deficient diets. Points of similarity are the symmetry of the lesions, their restriction to gray matter and their occurrence in periaqueductal and periventricular regions. Points of dissimilarity are the relatively extensive and severe lesions in the corpus striatum, the relative rarity and small size of the thalamic lesions and the relative absence of the vascular changes which have been considered so important a part of the process in polioencephalitis hemorrhagica superior.

4. Bender, L., and Schilder, P.: Arch. Neurol. & Psychiat. **29**:990, 1933.
5. Hiller, F.: Arch. Neurol. & Psychiat. **20**:145, 1928.

A comparison of the distribution of lesions of this type in various animals and in man is presented in table 2.

In comparing the histologic nature of the lesions in our animals with those of Wernicke's polioencephalitis hemorrhagica, we find first the need for clarification of one point: namely, the significance, if any,

TABLE 2.—*Comparison of the Distributions of the Lesions in Man and Various Other Animals*

Location	Man *	Monkey	Fox †	Rat ‡	Pigeon §	Pigeon ‖
Cerebral cortex	++	+	+	..	..	..
Septum pellucidum	++	..	..	..	..	..
Corpus callosum	+	..	..	..	..	..
Cerebellar cortex	+	+++	+++	..	x	..
Basal ganglions						
Caudate and putamen	+	++++	..	..	x	..
Globus pallidus	..	++	++	..	..	..
Thalamus	++++	++	++	..	..	x
Habenular nucleus	+	..	++	..	..	..
Substantia nigra	+	+	..	..	+	..
Hypothalamus:	++++	..	..	..	..	x
Dorsomedial nucleus	+++	..	..	..	..	..
Ventromedial nucleus	++++	..	..	..	..	..
Supraoptic nucleus	+	..	..	..	..	..
Corpora mamillaria	++++	++	..	..	..	x
Midbrain gray matter:	+++	..	..	..	..	..
Superior colliculi	++	..	+	..	..	..
Inferior colliculi	++	+++	+++	..	..	..
Nucleus centralis superior	..	++	..	..	..	..
Cranial nerve III (oculomotor) nucleus	++	+++	+++	..	x	x
Cranial nerve IV (trochlear) nucleus	+	..	+	..	x	x
Pons and medulla:						
Cranial nerve VI (abducens) nucleus	++	+++	..	++	..	x
Cranial nerve VIII (auditory) nucleus	+++	++	+++	++++	++	x
Cranial nerve X (vagus) nucleus	+++	+++	+++	..	..	x
Bechterew's nucleus	..	..	..	+++	..	..
Nucleus fasciculus solitarius	..	++	..	++++	..	..
Restiform body	..	..	+++	..	..	..
Inferior olivary nucleus	++	..	..	..	..	..
Cuneate nucleus and nucleus gracilis	..	..	+++	..	..	..
Locus caeruleus	+	..	..	..	..	..
Nucleus pontis	+	..	..	..	..	..
Deiters' nucleus	..	..	..	++++	..	..

+ to ++++ indicate rare to very common. x indicates that lesions were "present," frequency not stated.

* The data are drawn from: Bender and Schilder.[4] Hiller.[5] Campbell and Biggart.[7] Jolliffe and others.[8] Meyer, A.: J. Neurol & Psychiat. **7**: 66, 1944. Riggs, H. E., and Boles, R. S.: Quart. J. Stud. on Alcohol **5**: 361, 1944. de Wardener, H. E., and Lennox, B.: Lancet **1**: 11, 1947.

† The data are from: Evans, C. A.; Carlson, W. E., and Green, R. G.: Am. J. Path. **18**: 79, 1942.

‡ The data are from Prickett.[17]

§ The data are from Swank and Prados.[10]

‖ The data are from Alexander.[6]

of the capillary changes in the latter. Throughout the earlier literature on human and experimental Wernicke lesions, much emphasis was placed on the capillary dilatations, varicosities, and tortuosity, on

the endothelial proliferation and on the petechial hemorrhages. Alexander [6] decided that this was the primary lesion, with parenchymal degeneration a relatively less important result, and even adopted the benzidine stain for capillaries as the standard technic for studying this disease. However, the parenchymatous necrosis in human cases has received some emphasis by Campbell and Biggart [7] and Zimmerman.[8] Jolliffe and associates [9] stated that hemorrhages are not always present. Swank and Prados,[10] using the same species as Alexander (pigeon), decided that the parenchymal necrosis was primary and the vascular lesions secondary. Follis,[11] in discussing the methods and conclusions of Alexander, stated that Alexander "has postulated without any justification whatsoever, that thiamine possesses 'angiodegenerative properties'." Follis, in fact, doubted that Wernicke's encephalopathy is a result of thiamine deficiency alone and considers questionable the published data on this disease in man, the pigeon and the fox. Dunn [12] found hemorrhages in 60 per cent of thiamine-deficient mice, usually in the medulla, but no evidence of any vascular proliferation. Hemorrhages seemed to have a predilection for those areas which are normally quite vascular and have thin-walled blood vessels.

In our own animals the vascular changes were not found at all in the earlier and milder lesions and only in moderate degree in the more severe lesions of animals with moderately prolonged deficiency diet. Only in the animal with the greatest number of acute deficiency episodes (illustrated in figure 7) and the animal with a continuous prolonged deficiency state was the vascular change fairly prominent, consisting of dilatation, endothelial proliferation and an apparent true increase in the number of vessels and capillary budding in the corpus striatum. The vascular activity seemed to be a response to, rather than the cause of, the destruction of nerve tissue, being the principal attempt at repair observed.

Human vitamin deficiencies are usually multiple, and it is probable that most of the earlier experimental work on thiamine also involved other deficiencies. Therefore, it seems likely, by implication,

6. Alexander, L.: Am. J. Path. **16**:61, 1940.

7. Campbell, A. C. P., and Biggart, J. H.: J. Path. & Bact. **48**:245, 1940.

8. Zimmerman, H. M.: A. Research Nerv. & Ment. Dis., Proc. (1941) **22**:51, 1943.

9. Jolliffe, N.; Wortis, H. and Fein, H. D.: Arch. Neurol. & Psychiat. **45**:569, 1941.

10. Swank, R. L., and Prados, M.: Arch. Neurol. & Psychiat. **47**:97, 1942.

11. Follis, R. H., Jr.: The Pathology of Nutritional Disease, Springfield, Ill., Charles C Thomas, Publisher, 1948.

12. Dunn, T. B.; Morris, H. P., and Dubnik, C. S.: J. Nat. Cancer Inst. **8**:139, 1947.

that the vascular changes of human polioencephalitis hemorrhagica superior are either the result of other deficiencies or only a secondary occurrence in thiamine deficiency, and that the characteristic result of thiamine deficiency in man, primates and probably other animals is primary parenchymatous degeneration of subcortical gray matter.

Peripheral Neuropathy.—The absence of evidence of peripheral neuropathy is another item which deserves special mention and clarification. Contradictory reports on the relation of thiamine to neuritis have continued to appear during the past decade and are due in part to greater difficulties in dietary control in the earlier work, to effects of starvation in some cases and most of all to the diversity of criteria set up by various workers for the diagnosis of neuritis. In regard to criteria, we find at one end of the scale such generous interpretations as that of Lowry, Sebrell, Daft and Ashburn,[13] who diagnosed polyneuropathy when a rat became spastic and had an ataxic tonic convulsive seizure when dropped on its back from a 3 to 5 inch (7.5 to 12.5 cm.) height; or that of Prickett, Salmon and Schrader,[14] who diagnosed neuropathy on the basis of an increase in the amount of isotropic material in myelin sheaths, even though the Marchi and other stains were negative. At the other end of the scale, Swank and Prados[10] required alterations of axis-cylinders, as well as easily demonstrable degeneration of myelin sheaths, for the diagnosis of neuropathy.

In regard to starvation, always a potential factor in thiamine deficiency, degeneration of myelin may result from it alone, according to Williams and Spies,[15] Swank[16] and Swank and Prados.[10] Prickett, Salmon and Schrader,[14] using the polarized light technic, actually found slightly more alterations of myelin in rats fed adequate amounts of thiamine and limited as to food intake than in the acutely thiamine-deficient rats, although this did not hold true in chronic deficiency. Absence of any significant peripheral neuropathy in thiamine-deficient animals has been reported by Prickett[17] in rats, by Wechsler, Jervis and Potts[18] in monkeys, by Engle and Phillips[19] in chicks, by

13. Lowry, J. V.; Sebrell, W. H.; Daft, F. S., and Ashburn, L. L.: J. Nutrition **24**:73, 1942.

14. Prickett, C. O.; Salmon, W. D., and Schrader, G. A.: Am. J. Path. **15**:251, 1939.

15. Williams, R. R., and Spies, T. D.: Vitamin B_1 and Its Use in Medicine, New York, The Macmillan Company, 1938, chap. 4, p. 57.

16. Swank, R. L.: J. Exper. Med. **71**:683, 1940.

17. Prickett, C. O.: Am. J. Physiol. **107**:459, 1934.

18. Wechsler, I. S.; Jervis, G. A., and Potts, H. D.: Bull. Neurol. Inst. New York **5**:45, 1936.

19. Engle, R. W., and Phillips, P. H.: J. Nutrition **16**:585, 1938.

Wintrobe, Follis, Humphreys, Stein and Lauritsen [20] in pigs and by Dunn and associates [12] in mice. The suggestion that human peripheral neuritis is due to a multiple deficiency is made by participants in the discussion following the paper by Kolb and co-workers [21] and by Strauss.[22] Zimmerman [23] in 1939 referred to thiamine as the "proven" antineuritic vitamin, but in 1943 [6] he stated that it is probably, but not necessarily, the antineuritic vitamin in man. Meiklejohn [24] summarized the clinical and experimental reports up to 1940 and concluded that thiamine is not the "antineuritic vitamin." Follis [11] concluded that thiamine is not antineuritic in lower mammals but may possibly be so in birds. In summary, then, no histologic evidence of peripheral neuritis was found in these 7 monkeys, and this finding is in agreement with the results of many other recent investigations of experimental thiamine deficiency. Clinical evidence of sensory neuritis was not detected in our animals. However, the therapeutic value of thiamine in peripheral neuritis in man cannot be ignored, nor can we overlook the indispensable role of thiamine in normal nerve function, as recently summarized by Von Muralt.[25] It is possible that there is a physiologic defect that is not reflected in structural changes.

SUMMARY

Feeding of 7 rhesus monkeys a thiamine-deficient diet with widely spaced small thiamine supplements resulted in bilateral symmetric areas of degeneration, observed most commonly in the corpus striatum and seen also in the globus pallidus, substantia nigra, mamillary bodies, corpora quadrigemina, cerebellar cortex and the nuclei of the third, sixth, eighth and tenth cranial nerves. Capillary and endothelial changes were a relatively late finding and were interpreted as an attempt at repair of the injury. Associated with these lesions were profound weakness, ataxia and occasional focal signs of cranial nerve weakness or hyperirritability. No clinical or histologic evidence of peripheral neuropathy or of degeneration of fibers of the spinal cord was observed.

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20. Wintrobe, M. M.; Follis, R. H., Jr.; Humphreys, S.; Stein, H., and Lauritsen, M.: J. Nutrition **28**:283, 1944.

21. Kolb, L. C.; Wintrobe, M. M.; Mushatt, C.; Miller, J. L., Jr.; Lisco, H., and Stein, H. J.: Tr. Am. Neurol. A. **67**:189, 1941.

22. Strauss, M. B.: A. Research Nerv. & Ment. Dis., Proc. (1941) **22**:141, 1943.

23. Zimmerman, H. M.: Yale J. Biol. & Med. **12**:123, 1939.

24. Meiklejohn, A. P.: New England J. Med. **223**:265, 1940.

25. von Muralt, A.: Advances in Research and Applications, New York Academic Press, Inc., 1947, vol. 5, p. 93.

PATHOLOGIC CHANGES AFTER PARTIAL HEPATECTOMY

With Special Reference to Hepatic Necrosis in Protein-Depleted Rats

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THIS report is based on observations made during the course of experiments in which partial hepatectomy was performed on 230 rats. A detailed protocol was kept at autopsy of each rat that died or was killed, and histologic sections were prepared of the liver at operation and of the liver and certain other organs at the time at which an animal was killed. The analytic and metabolic data for which the experiments were designed have been reported elsewhere.[1] The most important pathologic finding is considered to have been a severe focal necrosis of the liver which appeared in some of the animals that had been partially depleted of protein before the operation.

METHOD

The animals used were all male Wistar rats weighing approximately 250 Gm. Details of diets and methods have been described elsewhere.[1] The operation of Higgins and Anderson,[2] which in our hands removed 69.4 ± 1.34 per cent of the liver, was employed in all but 12 animals. Ether anesthesia was used. Regeneration was studied after postoperative intervals of one to fourteen days. Tissue for histologic examination was fixed in 4 per cent formaldehyde solution and stained with hematoxylin and eosin and with sudan III for fat.

PATHOLOGIC CHANGES IN THE LIVER

In table 1 the animals are divided into six series according to their management. Fifty-six animals (series 1) came to operation in good nutrition, having been reared on a stock diet until one week before operation, when a synthetic diet containing 18 per cent or more of casein was substituted. No complications beyond occasional infection of a wound was observed among the 52 animals which survived operation. There were no postoperative deaths, and no gross

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From the Harrison Department of Surgical Research, University of Pennsylvania Schools of Medicine.

1. (*a*) Gurd, F. N.; Vars, H. M., and Ravdin, I. S.: Am. J. Physiol. **152**:11, 1948. (*b*) Vars, H. M., and Gurd, F. N.: ibid. **151**:391 and (*c*) 399, 1947.

2. Higgins, G. M., and Anderson, R. M.: Arch. Path. **12**:186, 1931.

or microscopic abnormalities were noted in the livers. Mitotic activity paralleled that reported by Brues, Drury and Brues.[3] Mitoses appeared between eighteen and twenty-four hours after operation, were still numerous at forty-eight hours, much fewer at four days and difficult to find thereafter. This sequence applied to both well nourished and protein-depleted animals. It was our impression that twenty-four and forty-eight hours after operation the mitoses were actually more numerous in the livers of protein-depleted animals than in those of the well nourished series.

Chemical analysis of the liver tissue removed at operation from the protein-depleted animals (series 2, 3, 4 and 6), which had been consuming a high carbohydrate diet and were not fasted, showed total lipid to be 6 to 8 per cent and glycogen 6 to 9 per cent.[1a] In gross appearance the liver tissue was paler than that of the protein-fed animals. Histologically, the liver cells were moderately

TABLE 1.—*Causes of Deaths Following Partial Hepatectomy in Various Dietary Groups of Rats*

Series	Pre-operative Diet	Operative Treatment	Rats Operated on	Number That Survived Operation	Number That Died Post-operatively	Causes of Postoperative Deaths: Hepatic Causes: Massive Necrosis	Causes of Postoperative Deaths: Hepatic Causes: Focal Degeneration	Causes of Postoperative Deaths: Other Causes
1	Adequate protein	Hepatectomy, 69.4%	56	52	0	0	0	0
2	Nonprotein 14 days	Hepatectomy, 69.4%	144	141	15	6	4	Pneumonia—2 Unknown—3
3	Nonprotein 28 days	Hepatectomy, 69.4%	6	6	1	0	0	Pneumonia—1
4	Nonprotein 14 days	Hepatectomy, 69.4%, and NaR*	6	6	2	0	2	0
5	Stock	Hepatectomy, 77%	6	5	0	0	0	0
6	Nonprotein 14 days	Hepatectomy, 77%	12	11	4	0	2	Pneumonia—1 Unknown—1
Total			230	221	22	6	8	8

* Sodium ricinoleate, 0.5 cc. of a 10 per cent solution per hundred grams of body weight, was injected subcutaneously.

large with apparently normal nuclei. The cytoplasm was extensively vacuolated, with no deep-staining basophilic particulate granules. Figure 1 illustrates such a specimen of tissue. The photomicrograph is identical in appearance with the photomicrographs of liver from hypoproteinemic dogs presented by Elman and Heifetz.[4] More recently, in an important contribution, Kosterlitz[5] illustrated histologic sections from the livers of rats fed protein-deficient diets which present the same appearance. In his analytic results Kosterlitz has shown that the cytoplasm as a whole suffers a decrease of substance in the protein-depleted state, and he has coined the expression "hypocytoplasmic liver" to describe this entity.

Figure 2 illustrates the histologic appearance when a fourteen day period of a nonprotein diet was followed by four days of starvation. The vacuolation of the

3. Brues, A. M.; Drury, D. R., and Brues, M. C.: Arch. Path. **22**:658, 1936.
4. Elman, R., and Heifetz, C. J.: J. Exper. Med. **73**:417, 1941.
5. Kosterlitz, H. W.: J. Physiol. **106**:194, 1947.

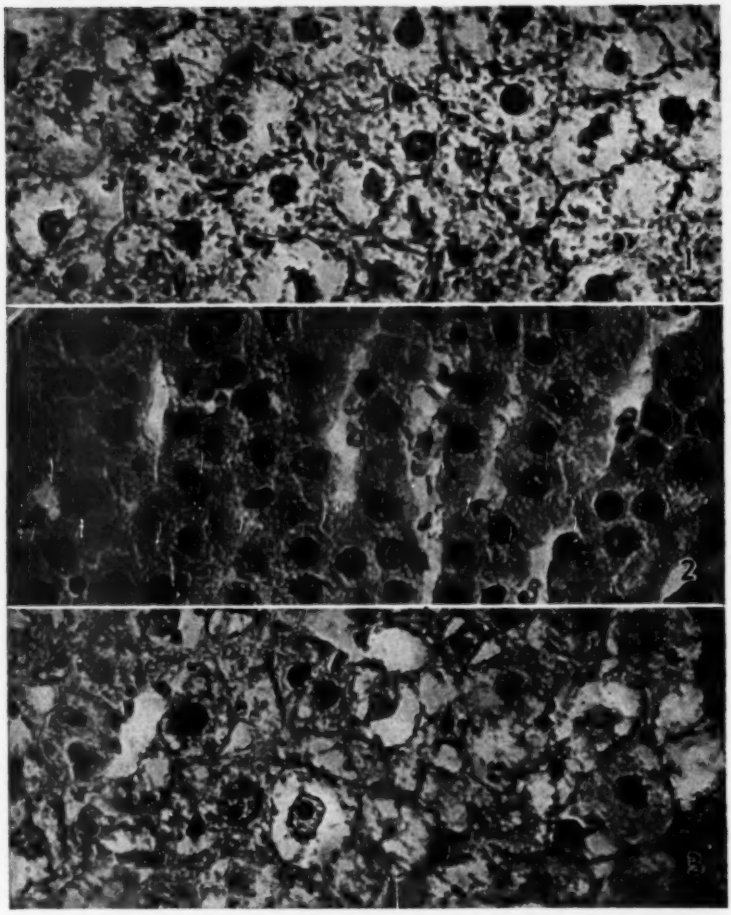

Fig. 1.—Section of liver (31A) of a rat fed a nonprotein diet for fourteen days but not fasted; × 800. Large cells, markedly vacuolated, are seen showing shreds of eosinophilic cytoplasm but no basophilic intracytoplasmic particles.

Fig. 2.—Section of liver (228B) of a rat which had undergone fourteen days of a nonprotein diet followed by four days of starvation; × 800. Note the reduction in the size of the cells as compared with those in figure 1; also, the loss of vacuoles and the smooth texture of the cytoplasm, without large granules.

Fig. 3.—Section (31B) from the same liver as that shown in figure 1, taken twenty-four hours after partial hepatectomy; × 800. Cells of varying size are seen, with marked vacuolation in some and evidence of active mitosis.

cytoplasm disappeared. Cytoplasmic particles were still absent, and the cells were much decreased in size.

The terminal histologic aspect of the liver during the first two days after operation is illustrated in figure 3. There was usually some increase in stainable lipid in addition to active mitosis. However, by analysis the lipid concentration never exceeded 9 per cent in either series 1 or series 2. Postoperative feeding of adequate amounts of protein [1b] led to recovery of the staining properties and reappearance of cytoplasmic particles as illustrated in figure 4. Two weeks after operation the regenerated liver tissue differed from that of controls not operated on in two respects. First, the naked eye could perceive the increase in size of the regenerated lobules on either the serosal or the cut surface of the liver. Second, the organ was grossly soft and friable, and microscopically the supportive stroma was sparse and immature.

Series 2 of table 1 shows the outcome of 69.4 per cent hepatectomy in 144 rats prepared for operation by being restricted to a nonprotein diet for fourteen

TABLE 2.—*Pathologic Observations in Livers of 6 Rats Showing Massive Necrosis*

Rat	Post-operative Survival, Hr.	Time of Necropsy	Gross Observations	Microscopic Observations				
				Necrosis	Hemorrhage	Inclusion Bodies	Mitosis	Leukocytic Infiltration
98	26	<5 hr.	Pale, yellow, with large hemorrhages	++++	++++	++++	0	±
116	76	<1 hr.	Moderately pale, with small hemorrhages	++	+	0	0	+
126	47	2 min.	Pale, yellow, with small hemorrhages	++	+	++++	±	++
135	29	*	Pale, gray, with large hemorrhages	++++	++++	++++	0	±
173	20	30 min.	Pale, gray, with large hemorrhages	++++	+++	++++	0	±
273	24	3 min.	Pale, yellow, with multiple small hemorrhages	++++	++++	++++	0	+++

* This rat was killed while moribund.

days. Three of these died at operation, while 15 died subsequently. Ten of the 15 which succumbed in the postoperative period had degenerative changes in the liver. Six of these had hemorrhagic necrosis of the liver.

The observations on these 6 animals are analyzed in table 2. The postoperative course was similar in each case. All animals recovered from the immediate effects of the operation and were generally walking about for several hours after recovery from the anesthetic. They were uniformly anorectic and ate nothing between operation and death. During the second or third twelve hour period they became progressively less active. Respirations became rapid, and before death they were generally quite unresponsive to stimulation. In an occasional animal terminal convulsions of a generalized clonic type developed. Death usually occurred, as shown in table 2, during the second day. The timing and the pattern of events were quite similar to the so-called "liver death" of clinical experience.[6]

6. Boyce, F. F.: The Role of the Liver in Surgery, Springfield, Ill., Charles C Thomas, Publisher, 1941.

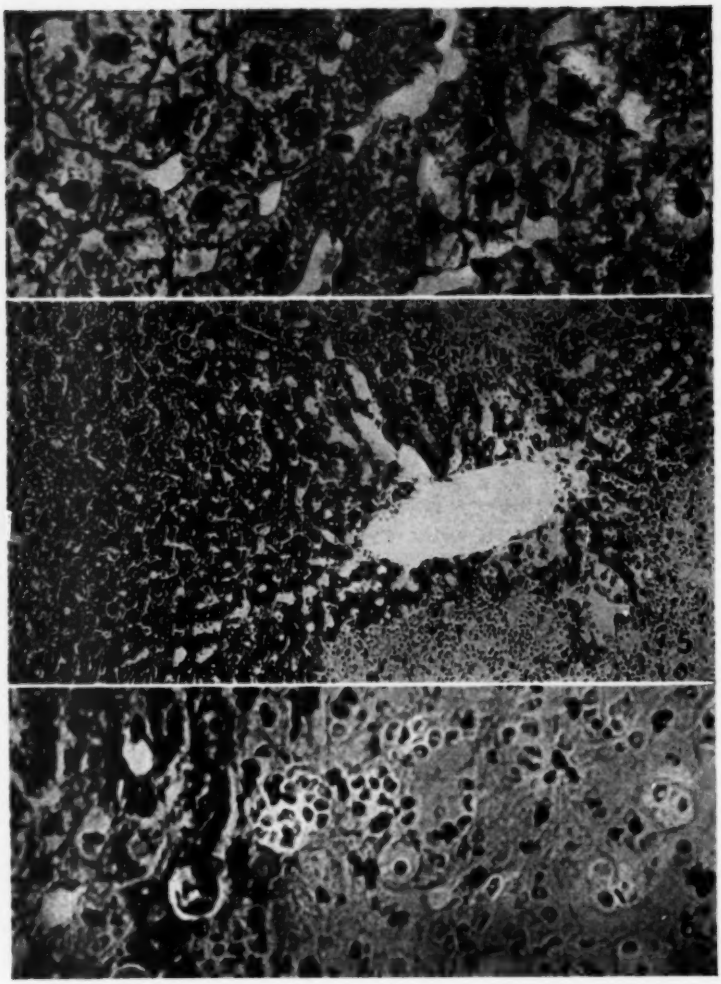

Fig. 4.—Section of liver (127B) of a rat which was fed a nonprotein diet for fourteen days, then partially hepatectomized and finally fed a diet containing 18 per cent casein for fourteen days after operation. The appearance is that of liver of a normal protein-fed rat. The cells are large; the cytoplasm stains heavily and contains an abundance of basophilic granules.

Fig. 5.—Liver of rat 273 (table 2), whose death occurred twenty-four hours after operation, with autopsy being made at once; Giemsa stain; × 150. Areas of massive necrosis are seen, with a relatively intact collar of liver tissue about the central vein.

Fig. 6.—Portion of section shown in figure 5; Giemsa stain; × 700. Details of the necrotic area may be seen. Several inclusion bodies are evident in a corner of the section.

The necrotic livers described in table 2 were grossly pale except for the flame-shaped hemorrhagic areas, which appeared to involve indiscriminately all areas of the liver remnant.

The histologic picture was the same in all cases, differences being only of degree. Figures 5 and 6 show a characteristic section under low and high magnification. The massive character of the necrotic lesion is evident. Much of the necrotic parenchyma is involved by infarction due to presence of blood. The degree of leukocytic infiltration of the infarcts varied from animal to animal. The lesions appeared to be midzonal in origin, and often the only intact parenchyma in a lobule was a collar about a central vein.

Vacuoles containing spherical inclusions were prominent in all but 1 liver. These were eosinophilic and hyaline. The smaller of these bodies were distinctly intracellular and showed no particulate structures. Many larger ones appeared to lie outside the liver cells and to contain red blood cells. It was impossible to determine unequivocally whether some were formed outside the liver cells, or whether all originated in the cytoplasm of the parenchyma and later broke out of the cells as the latter disintegrated. In 5 of the 6 livers mitotic figures could not be found even in undamaged parenchyma; in the sixth they were extremely rare. Histologically, fat was always present in the uninvolved tissue but not always in large amount.

Four other rats in series 2 showed at death a focal degenerative lesion of the liver without hemorrhagic infarction of a type which might be classified as focal coagulation necrosis. Small, indiscriminately scattered areas of pale, degenerated cells, showing no nuclear material characterized this lesion. Inclusion bodies were not seen. These deaths occurred later than those in the cases of hemorrhagic necrosis, from two to seven days after operation. Mitoses were few but were not so conspicuously absent as in the hemorrhagic livers.

Series 3 of table 1 consisted of a group depleted of protein for twenty-eight days before operation and restricted to the nonprotein diet for eight days postoperatively. No hepatic lesions were found in this series, and there was no notable loss of the ability of the liver to regenerate.[1a] Series 4 received sodium ricinoleate, 0.5 cc. of a 10 per cent solution per one hundred grams of body weight being injected subcutaneously at the time of operation. This treatment superimposed a sterile abscess on the stress of depletion and partial hepatectomy. The animals were more severely affected than by the operation alone. Two of the 6 died within thirty-six hours with evidence of focal degenerative changes in the liver but no extensive necrosis.

Series 5 and 6 were submitted to an operation in which not only the median and right lateral lobes but also the caudate lobe was removed.[2] The operation was found to involve approximately 77 per cent removal of the liver. The procedure did not disturb the well nourished animals in series 5 but was definitely a most severe strain on the protein-depleted rats. In series 6 all animals were seriously ill; all had bile pigments in the urine and an unusual amount of extravasated blood in the laparotomy wounds. Eleven animals survived operation, 4 of which died after between sixteen and forty-eight hours. Focal degenerative lesions were observed in 2. One survivor which appeared to be recovering well when killed at forty-eight hours provided a unique histologic observation: a liver involved by moderately extensive hemorrhagic necrosis with extremely active mitosis in the intact tissue. This is the only instance suggesting that an animal can recover from an established hemorrhagic necrosis of this type.

LIVER PROTEIN REGENERATION IN NECROTIC LIVERS

Three of the livers shown in table 2 were analyzed for protein by the methods previously described.[1a] Rat 116 had a postoperative liver protein increment of 0.08 Gm. per hundred grams of initial body weight. The expected increment at seventy-six hours had been found from previous experiments to be between 0.10 and 0.14 Gm. Rat 126 showed an increment of 0.07 Gm. against an expected figure of 0.10 Gm. at forty-eight hours. Rat 135 had gained 0.10 Gm. in twenty-nine hours, which exceeded the expected figure of 0.04 Gm., but this liver, unlike the other 2 livers, was heavily infiltrated with blood. The findings in rats 116 and 126, in which the analytic picture was not greatly obscured with bloody infiltration, provide a slender correlation with the apparent suppression of mitotic activity observed in the histologic sections. It is suggested that the necrosis and death were related to a failure of the organ to initiate a prompt regenerative response.

No evidence was found of an increase of extractive (nonprotein) nitrogen in these livers, which is in conformity with the findings of Himsworth and Glynn.[7] in their dietetic necrosis. Fat and glycogen analyses were not done on any of the individual animals listed in table 2.

PATHOLOGIC CHANGES IN OTHER SITES

Thymus.—This organ was not weighed at autopsy but was examined grossly in every case and frequently histologically. Gross observation showed that it decreased in size during a fourteen day period of a nonprotein diet, although even six weeks on this diet failed to cause extreme atrophy. However, in the animals depleted of protein for fourteen days and then partially hepatectomized, a sudden and extreme reduction in the size of the gland was found to occur. Within forty-eight hours after operation it was often difficult to identify the organ at all, and sections showed an extreme reduction in the size and the number of lymphoid follicles, with considerable reticulum which was virtually empty of lymphoid cells. This condition was found to persist up to fourteen days after operation unless the animal was realimented on a protein-containing diet. The question is raised whether lymphoid tissue, as exemplified by the thymus, may not contribute to the internal shifting of body nitrogen to the liver, which must occur when the latter organ undergoes regeneration in the absence of exogenous protein.[8]

Kidneys.—No hemorrhagic or degenerative lesions were noted in the kidneys. Many protein-depleted animals showed mottled yellow areas on the surface of the organ and extending part way through the cortex. These areas were especially marked in series 6, which were the most severely affected of any animals. With fat stains such areas were found to contain pathologic amounts of fat, localized in the cells of the proximal convoluted tubules.

Adrenal Glands.—No lesions were found under any circumstances tested. The only groups which showed any gross increase in the size of the adrenal glands were those subjected postoperatively either to total starvation or to restriction of their caloric intake. The adrenal glands of animals fed the nonprotein diet were small and appeared to remain so after the operation. In general, the glands of rats in a good nutritional state were larger than those of animals which were protein depleted, but there was no gross evidence of hypertrophy of the adrenal glands after the operation, nor of any change in the microscopic appearance.

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7. Himsworth, H. P., and Glynn, L. E.: Biochem. J. **39**:267, 1945.
8. White, A., and Daugherty, T. F.: Endocrinology **41**:230, 1947.

Laparotomy Wounds.—In the majority of the cases in which a rat was killed sections of the site of the laparotomy wound were made at the time of death. Little can be said about differences in healing which might be attributed to the various diets. Even in animals fed a nonprotein diet throughout the experiment the wound appeared to heal as well as in those which were adequately fed. So far as could be seen with hematoxylin and eosin staining, the only difference between the two groups was an appearance of greater cellularity in the fibrous scars of the protein-depleted animals. There was no difference in the incidence of wound infection. No evisceration occurred.

COMMENT

The necrotic lesions observed after partial hepatectomy in the livers of a small percentage of our animals are the first of their type to be reported. They occurred only in rats which were partially hepatectomized while in a state of partial protein depletion. It is considered that the necrosis appearing in the liver remnant is related in some way to the protein-depleted state.

It has been shown previously that a liver low in protein is especially susceptible to necrosis following chloroform anesthesia.[9] The same observation applies to the liver of an animal in which the protein stores have been decreased.[10] In our rats we have found that the fourteen day preoperative period of a nonprotein diet decreased the liver protein by approximately 40 per cent.[10a] Accordingly, the standard surgical ablation of 70 per cent of the remaining liver resulted in a considerably greater net reduction of liver protein than was found when the same operation was performed on well nourished animals. It is possible that the severe reduction of liver substance achieved in the protein-depleted rats created a set of circumstances in which a "spontaneous" type of hepatic necrosis might occasionally make its appearance.

The basic causation of the necrosis is not explained by the related protein depletion. It is quite likely that the extreme attenuation of liver function which must have occurred in our animals led to a vicious cycle of events which ended in the destruction of an organ usually capable of maintaining at least structural integrity up to the time of death. For example, it could be postulated that suppression of the formation of prothrombin might have contributed to the hemorrhage of the liver's own parenchyma. Infection might well have played a part in the necrosis. Indeed, the lesion bears a resemblance to the focal necrosis described by earlier authors as occurring in overwhelming infections, especially in enteric diseases, such as typhoid.[11] It is emphasized that we have no direct evidence as to the part played by prothrombin

9. Goldschmidt, S.; Vars, H. M., and Ravdin, I. S.: J. Clin. Investigation **18**:277, 1939.

10. Miller, L. L., and Whipple, G. H.: Am. J. M. Sc. **199**:204, 1940.

11. Mallory, F. B.: J. M. Research **6**:264, 1901.

deficiency, infection or any other specific factor in the causation of the lesion.

The finding of eosinophilic inclusion bodies suggests a virus infection. However, it is known that inclusions are not necessarily a definite proof of virus disease, for they are also found in necrosis of the liver after tannic acid treatment of burns [12] and in high altitude anoxia and in carbon monoxide poisoning.[13] There is every likelihood that the appearance of inclusion bodies may represent a phase of physicochemical disintegration of the dying cell without specific etiologic significance.

The lesion described by Glynn and Himsworth [14] differs from ours in that the necrotic foci were not characterized by hemorrhage. Nevertheless, the two lesions appear to be initiated by a dietary insufficiency, specifically of protein or a component of protein.

Two facts in connection with the hepatic necrosis and death of the protein-depleted animals appear to be demonstrated by our observations. First, the animals were in a state of precarious compensation as to liver function for about forty-eight hours after operation. That is, the attenuation of liver substance was near the minimum compatible with survival. This impression was tested further with the experiment shown in series 6 of table 1, in which 12 protein-depleted rats were subjected to 77 per cent hepatectomy. Evidences of liver failure were abundant in this series, namely, the increased lassitude and anorexia, the bile pigments constantly appearing in the urine, the increased bleeding tendency and the higher mortality.

The second fact is that there was no mitotic activity in the necrotic livers detailed in table 2. The fragmentary analytic data already described for 3 of these animals support the conclusion that death was related to a failure of the hyperplastic regenerative response. It may be possible that the level of liver function left to the animals of our standard protein-depleted series was not only near the minimum required for survival but actually below that minimum and that survival was conditional on a certain degree of regeneration being successfully effected within about forty-eight hours. It is probable that in the first hours after operation the liver remnant fell behind in the performance of its essential metabolic work but that in the majority of animals it increased its capacity through regeneration in time to catch up with the immediate demands before the consequences of deficiency became irreversible. In the animals in which the regenerative effort was inadequate, death occurred about the second day.

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12. Belt, T. H.: J. Path. & Bact. **48**:493, 1939. Duffin, J. D.: Canad. M. A. J. **47**:138, 1942.

13 Kritzler, R. A.: War Med. **6**:369, 1944.

14. Glynn, L. E., and Himsworth, H. P.: J. Path. & Bact. **56**:297, 1944.

We are not in a position to present studies of metabolites circulating in the blood to support this interpretation. We feel, however, that the observations are of interest and that the protein-depleted preparation described is of potential usefulness in the experimental study of hepatic insufficiency.

SUMMARY

Pathologic changes observed in the livers of 230 rats which were submitted to partial hepatectomy are reported.

A massive hemorrhagic necrosis of the liver is described, which occurred during the second day after operation in animals which had been previously partially depleted of protein through being restricted to a nonprotein diet for fourteen days.

The livers involved in this necrosis showed failure of the usual regenerative response. Mitotic activity was conspicuously absent, and fragmentary analyses suggested that the regeneration of new liver protein was retarded.

Evidence has been discussed to support the hypothesis that the functional liver tissue remaining in the protein-depleted rats after 70 per cent hepatectomy was inadequate to support life and that survival was conditional on a prompt regenerative response.

Some observations on the gross and histologic changes in the thymus, the kidneys, the adrenal glands and the laparotomy wounds are also included. A rapid involution of the thymus was noted in protein-depleted rats after partial hepatectomy.

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UNUSUAL HAMARTOMA OF THE LUNG IN A NEWBORN INFANT

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THE TERM "hamartoma" was coined in 1904 by Albrecht,[1] who defined it as comprising "tumor-like malformations in which occur only an abnormal mixing of the normal components of the organ. The abnormality may take the form of a change in quantity, arrangement or degree of differentiation, or may comprise all three. The deduction to be drawn from histologic examination of these formations is that they have originated in abnormal mixing of their development." In the cases that he described the lesion was in the liver, and he did not describe the type of pulmonary malformation under discussion. However, since 1904, pulmonary lesions which had previously been referred to by a variety of names but which met the criteria of Albrecht's definition began to be increasingly termed hamartoma.

Hamartoma of the lung is uncommon. The subject has been reviewed by Hickey and Simpson,[2] Verga,[3] McDonald, Harrington and Clagett[4] and Simon.[5] In 1944 McDonald and associates[4] collected 73 cases of the chondromatous type of hamartoma of the lung reported up to that time and added 23 similar cases of their own. From 1944 to the present 11 cases of chondromatous hamartoma of the lung have been reported.[6] Simon,[5] in a recent review of hamartoma of the lung has collected 25 cases of the hemangiomatous type. This brings the total number of reported cases of hamartoma of the lung to 132, of

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This study was aided by a Fellowship from the Dazian Foundation for Medical Research.

1. Albrecht, E.: Verhandl. d. deutsch. path. Gesellsch. **7**:153, 1904.
2. Hickey, P. M., and Simpson, W. H.: Acta radiol. **5**:475, 1926.
3. Verga, P.: Pathologica **24**:1, 1932.
4. McDonald, J. R.; Harrington, J. W., and Clagett, O. T.: J. Thoracic Surg. **14**:128, 1945.
5. Simon, M. A.: Am. J. M. Sc. **216**:33, 1948.
6. (*a*) Cid, J. M.: Arch. Soc. argent. de anat. norm. y pat. **2**:199, 1940; cited by Itoiz.[6e] (*b*) Bianchi, A. E., and Etchegoyen, H.: An. Inst. modelo de clin. med. **24**:405, 1943. (*c*) Latienda, R. I.: Arch. Soc. argent. de anat. norm. y pat. **8**:73, 1946. (*d*) Moreno, G.: Bol. y trab., Acad. argent. de cir. **30**:526, 1946. (*e*) Itoiz, O. A.; Latienda, R. I., and Murray, A. J.: Arch. Soc. argent. de anat. norm. y pat. **8**:223, 1946. (*f*) Sassaroli, S.: Ann. radiol. diag. **16**:415, 1942. (*g*) Simon, M. A., and Ballon, H. C.: J. Thoracic Surg. **16**:379, 1947.

which 107 appeared to represent an abnormal mixing of the elements of the bronchial wall and 25 apparently represented an abnormal development of the vascular components of the lung. Since this report is concerned with a case that is apparently related to the former group, no further reference to hemangioma of the lung need be made.

The so-called chondroma of the lung is reported as occurring in from 0.027 per cent [6e] to 0.25 per cent [4] of routine autopsy cases. Among 84 cases in which sex was indicated there were 61 males and 24 females. In the majority of instances the chondromatous tumor-like masses were incidental findings at autopsies. They were usually subpleural in location and in some instances had led to an erroneous roentgen diagnosis of Ghon tubercle. The lesions were usually small and ranged in size from a few millimeters to 3 or 4 cm. in diameter. However, McDonald and associates [4] mentioned a case in which the mass occupied the entire pleural cavity. Only in relatively few of the cases reported in the literature did the tumor reach a size sufficient to cause symptoms requiring surgical intervention.[7]

Hamartomas of the so-called chondroma type are described in general as being dense, somewhat hard, lobulated, bluish gray to white and having on section the general appearance of a true chondroma, but microscopically islands of epithelium, fetal fat, fibrous tissue and other features are found which betray their true nature.

Cancerous changes of lesions of this type are apparently rare. Greenspan [8] described a case of pulmonary osteochondrosarcoma and in his review suggested two possibilities as to the origin of the tumor. It was thought that it might have represented either a cancerous change of a preexisting hamartoma or that it was a true osteochondroma. Simon and Ballon [6g] described local cancerous features in their case of hamartoma. It is perhaps of interest to mention the cases reported by Cid.[6a] Of the 2 patients described, the first, a 78 year old man, died of pulmonary edema and a branchiogenic cancer of the right cervical region. A small hamartoma was found in the lung. The second, a 56 year old man, died of a bronchiogenic carcinoma, which was located in the hilar region of the left lung. At autopsy a small hamartoma was also found in the subpleural region of the lower lobe of the left lung.

The ages of the entire series of 107 patients with chondromatous hamartoma reported in the literature range from 21 to 78 years. A hamartoma of the lung of unusual though somewhat similar type occurring in a newborn infant is therefore considered to be of sufficient interest to report.

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7. McDonald and others.[4] Simon.[5] Sherwood, K., and Sherwood, H.: Journal-Lancet **52**:395, 1932.

8. Greenspan, E. B.: Am. J. Cancer **16**:603, 1933.

REPORT OF A CASE

A baby girl was born during the twenty-eighth week of pregnancy at 6:10 a.m. on March 8, 1948. She required extensive resuscitation, and only after twenty-five minutes of effort were spontaneous respiratory movements established, and these were irregular. In a short while these gradually diminished, and the infant died one hour after birth. The mother was a 21 year old primipara. The labor was of spontaneous onset and uncomplicated. The presentation was vertex.

Autopsy.—The infant weighed 1,516 Gm. and measured 52 cm. crown-heel and 38 cm. crown-rump. The heart weighed 11 Gm., and its epicardial surface

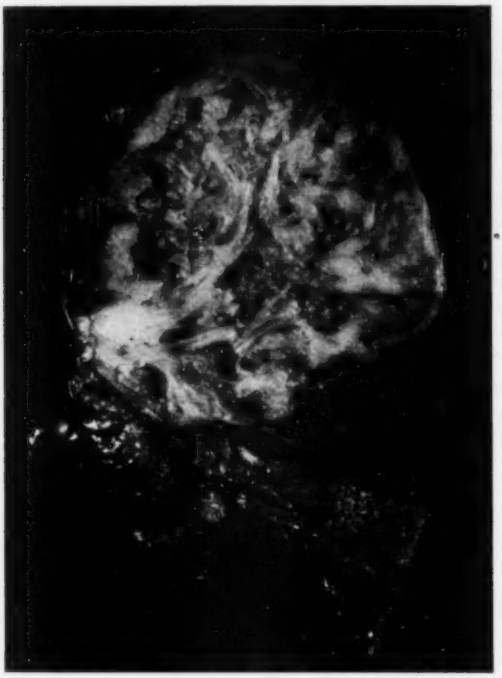

Fig. 1.—Hamartoma occupying almost the entire upper lobe of the right lung. A small portion of the middle lobe of the lung is also shown.

presented a few small petechial hemorrhages. The remaining organs, except for the lungs, were not remarkable.

The entire left lung weighed 15 Gm. and was atelectatic but otherwise not remarkable. The right lung weighed 50 Gm. and was partially aerated. The upper lobe (fig. 1) was full, rubbery and firm in consistency, and the pleural surface was blotchy brown. On section this fulness in the upper lobe was seen to be due to a spherical, circumscribed but nonencapsulated mass, 3.5 cm. in diameter, occupying almost the entire lobe, having a margin of compressed lung

tissue near the interlobar fissure. The cut surface was firm and pink with coarse whorls and interlacing bands of white fibrous tissue in which no cartilaginous component could be distinguished on gross examination. No large bronchi were present within the mass. The residual lung tissue of that lobe was collapsed.

Microscopic Examination.—The normal structure of the upper lobe of the right lung was completely altered and replaced by wide interlacing bands or bundles of tissue, some of which were seen in cross section as islands (fig. 2). They were composed of streaming lines of uniform elongated cells in parallel arrangement separated by sparsely distributed fibers. Their cytoplasm was thin; their nuclei,

Fig. 2.—A representative section of the hamartoma showing fibrous tissue trabeculae with dilated capillaries, islands of cartilage and bronchiolar structures interspersed through the fetal lung tissue. × 24.

elongated, oval and vesicular. These cells resembled fibroblasts. The delicate thin fibers proved, in sections stained with Van Gieson's stain, to be collagen. Irregularly scattered throughout these bands were rounded, oval or irregularly shaped small islands of immature cartilage, and more rarely areas of fetal fat. Scattered here and there in the fibrous bands were channels lined by respiratory epithelium, but no lymphoid tissue was seen. The intervening lung tissue was fetal in type. Portions of the bronchiolar mucosa were plicated, and their walls were in apposition. There was marked congestion of the capillaries, and one small area of hemorrhage was present.

The cause of death appeared to be prematurity, complete atelectasis of the left lung and partial atelectasis of the right lung, complicated with a hamartoma of the upper lobe of the right lung.

COMMENT

It is evident that the lesion in the upper lobe of the right lung in the case reported represents a hamartoma according to Albrecht's original definition, being in essence composed of masses of immature mesenchymal tissue, fibrous tissue, fetal fat, cartilage and imperfectly formed bronchiolar structures inextricably mixed up with more normally developed lung tissue. It presents none of the usual histologic features of a true tumor, and it is unquestionably benign in appearance. The small proportion of cartilage and much larger proportion of fibrous tissue elements set this hamartoma apart from the majority of those reported. In the latter, cartilage of fetal or of adult type usually composed the major portion of the malformations. In 3 exceptional cases of McDonald and associates [4] the anomaly had no cartilage.

Whereas hamartoma has not hitherto been reported as occurring earlier than the age of 21 years, the expectation that it should be discoverable at any time after birth is inherent in the concept of the hamartomatous malformation. That cases have not been reported heretofore in which the earlier age groups were concerned seems extraordinary. In any event the present case emphasizes the possibility that hamartoma may present itself as a clinical problem even in the neonatal period. If recognized as the cause of serious clinical manifestations, it should be entirely amenable to surgical removal.

SUMMARY

An unusual hamartoma, of fibrochondromatous type, involving almost the entire upper lobe of the right lung of a newborn premature infant is presented.

ABSENCE OF THE PULMONARY ARTERY: A NEW CLASSIFICATION FOR PULMONARY ARTERIES OF ANOMALOUS ORIGIN

Report of a Case of Absence of the Pulmonary Artery with Hypertrophied Bronchial Arteries

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ANOMALIES of the pulmonary artery occur rather frequently in congenital heart disease. These have been classified as stenosis or atresia of the pulmonary artery (truncus solitarius aorticus), persistent truncus arteriosus communis or patent ductus arteriosus. There is, however, a group of anomalies which we believe cannot be properly classified under any of the diagnoses named. For this group we propose a new classification, absence of the pulmonary artery. We have such an anomaly to report, and we believe that a consideration of its genesis and diagnosis will justify the separation of this from the other anomalies of the pulmonary artery.

REPORT OF CASE

The patient was a 10 month old Negro boy who was born April 24, 1942 and was first seen in the infant welfare clinic at the age of 6 weeks. There were no complaints at that time, and examination was reported to show no significant abnormalities. Two months later rapid respiration was noted, and a systolic murmur was found over the entire precordium. A roentgenogram of the chest showed enlargement of the heart, which had a well rounded left ventricle, and widening of the vessels of the mediastinum (fig. 1). The patient was followed at frequent intervals, and his condition remained unchanged. He died suddenly at home, Feb. 22, 1943, and the only history obtainable at the time of autopsy was that he had shown symptoms of a "heavy cold." The abnormalities noted at autopsy aside from those of the heart were: left lobar pneumonia with bilateral pleural effusion; acute splenic tumor with enlargement of the mesenteric and mediastinal lymph nodes; acute passive congestion of the liver, and a small congenital umbilical hernia.

The heart was normal in position but appeared moderately enlarged and weighed 95 Gm. The two sides of the heart were of equal size. The right atrium

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received the venae cavae and the coronary sinus and emptied into the right ventricle through a normal tricuspid valve. The left atrium received the right and left pulmonary veins, of usual size, and emptied into the left ventricle through a normal bicuspid valve. The interatrial septum was intact. There was hypertrophy of both ventricles, relatively greater on the right, so that the ventricular cavities were of approximately equal size. The myocardium measured 9 mm. in thickness at the base of the left ventricle and 8 mm. at the base of the right ventricle. There was a large defect at the base of the interventricular septum, 1 cm. in diameter, with the aorta overriding this defect, approximately one third to the left and two thirds to the right. The aorta was greatly dilated at its origin, its ring measuring

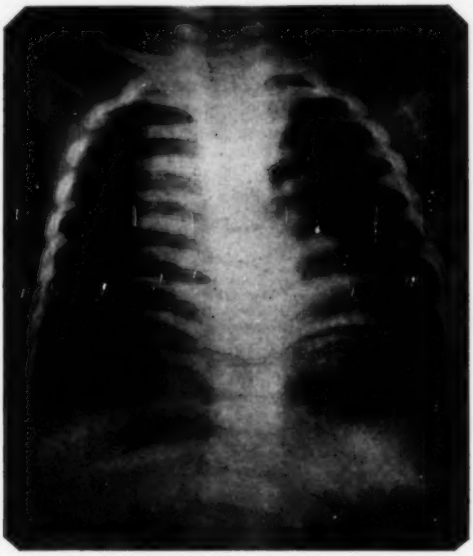

Fig. 1.—A roentgenogram showing cardiac enlargement, the typical "coeur en sabot" outline of the heart and remarkable widening of the mediastinal shadow. The hilar shadow is obscured on the right side but is normally prominent on the left.

5 cm. in circumference, and it presented three normal valve cusps, the coronary arteries arising from the right and left anterior sinuses. There were no other vessels arising from the heart, and there was no evidence of even a rudimentary pulmonary valve. The pulmonary artery was not present, nor was there any other vessel or remnant of a vessel which could represent the pulmonary artery. The ductus arteriosus was absent. The aorta assumed its normal course and gave rise to its usual branches. The bronchial arteries arose in their normal position from the descending aorta but were tremendously dilated and hypertrophied, being of about the same size as the celiac artery. They entered the lungs in close association with the posterior walls of the bronchi and constituted the lungs' sole supply

of arterial blood. Dissection of the hilus of each lung revealed that there were no other arteries entering the lung, and confirmatory evidence of this was obtained on microscopic examination of sections of the lung, which failed to show the presence of arteries other than the dilated bronchial arteries. Microscopic sections of the heart also showed hypertrophy and fragmentation of the muscle fibers.

The anatomic diagnosis of the cardiac defects follows: absence of the pulmonary artery; compensatory dilatation and hypertrophy of the bronchial arteries; dextroposition of the aorta ("rider" position); basal interventricular septal defect; dilatation of the ascending aorta; cardiac hypertrophy.

Figure 2 is a semidiagrammatic representation of the essential structural defects.

EMBRYOLOGIC CONSIDERATIONS

A consideration of the embryonal mechanism involved in the production of anomalies of the heart is essential to a correct interpretation and appreciation of the defects as seen at autopsy, and it is through

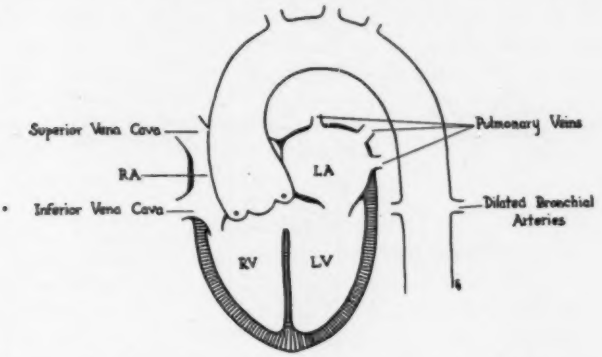

Fig. 2.—A diagrammatic representation of the heart showing absence of the pulmonary artery, hypertrophied bronchial arteries, dextroposition of the aorta and an interventricular defect.

such studies that the array of seemingly heterogeneous defects can be welded into pathologic and clinical entities. The fundamental lesion in our case was an absence or an early involution of the primitive sixth aortic arch, from which the normal pulmonary artery and ductus arteriosus develop. If the sixth arch had continued its usual development until the pulmonary artery was established, then any subsequent arrest of growth would have led to the more common stenosis or atresia of the pulmonary artery in which some remnant of the vessel is present. In cases of atresia the artery may be represented by no more than a thin fibrous band which may extend toward but not even reach the heart, as was found in one of our previous cases.[1]

1. Manhoff, L. J., Jr., and Howe, J. S.: Am. Heart J. **29**:90, 1945.

The development of the pulmonary artery of the early embryo has been excellently described by Huntington,[2] and a knowledge of the essential steps involved will allow a better understanding of the various defects that result from arrested development at different stages. The first important consideration is that the pulmonary vascular bed is established independently of the sixth arch and is not dependent on that vessel for its development. The pulmonary plexus in its early stages is connected to the ventral branches of the dorsal aorta. As its growth progresses, it sends out a branch cranially which joins with the free extremity of the ventral root of the sixth aortic arch, and its connections

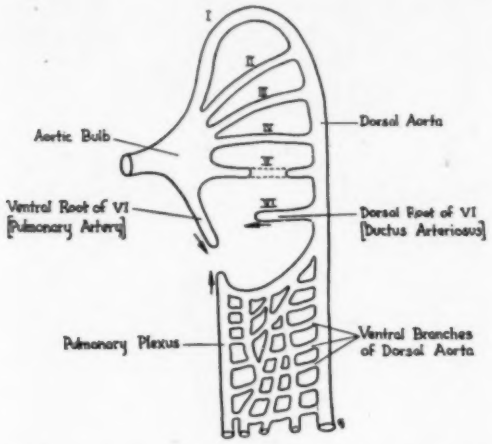

Fig. 3.—A diagram of the early stage of development of the pulmonary artery preceding the completion of the sixth arch (redrawn from Huntington[2]). Note that the pulmonary plexus develops independently of the sixth arch, and that it sends a vessel upward to join the ventral branch of the sixth arch. If the ventral branch were absent, this vessel could unite with the dorsal root, and if the entire sixth arch were absent the circulation in the pulmonary plexus could be maintained by the ventral branches of the aorta (usually the bronchial arteries).

with the dorsal aorta are later lost (fig. 3). The dorsal root of the sixth arch joins the ventral root just distal to the aortic bulb, thus establishing a complete arch but leaving a free extremity of the ventral root to be joined by the cranial branch of the pulmonary plexus to complete the pulmonary artery. The dorsal root of the left side persists along with the left fourth arch (which forms the normal left arch of the aorta) as the ductus arteriosus, while the right dorsal root disappears along with the right fourth arch. The aorticopulmonary septum arises

2. Huntington, G. S.: Anat. Rec. **17**:165, 1919.

from the angle between the fourth and sixth arches and grows toward the heart, dividing the common truncus arteriosus into the separate aorta and the main trunk of the pulmonary artery.

Depending on the stage at which this process is interrupted, several variations of the pulmonary artery are possible. Impaired growth of the established pulmonary artery will lead to stenosis or atresia of the artery, as already mentioned, leaving a recognizable remnant of the vessel. Incomplete development of the aorticopulmonary septum will fail to separate the trunks of the aorta and the pulmonary arteries, resulting in a persistent truncus arteriosus communis. If there is failure of the ventral root of the sixth arch, the dorsal root (future ductus arteriosus) may establish or maintain continuity with the pulmonary plexus and the pulmonary artery will then appear to rise from the arch of the aorta. If there is absence of the entire sixth arch, the pulmonary plexus will maintain its originl connections with the ventral branches of the dorsal aorta and the lungs will be supplied through bronchial or other arteries. The aforementioned developmental failures may be associated with other mechanisms, such as persistence of normally obliterated parts of the dorsal aorta, persistence of parts connecting the pulmonary plexus with more caudal ventral branches of the aorta, or other secondary changes, so as to give rise to various anomalous vessels supplying the lungs.

ANALYSIS OF CASES

There is some disagreement in the literature about the proper classification and diagnosis of certain types of cases, namely those in which there is only a single arterial trunk arising from the base of the heart. In those cases in which the single trunk is a pulmonary artery with an atretic aorta (truncus solitarius pulmonalis), or an aorta with an atretic pulmonary artery (truncus solitarius aorticus) little difficulty is encountered, as these anomalies are easily recognized. Consequently we may eliminate the atresias from our consideration.

When the question arises whether the single trunk is a persistent truncus communis or simply a normal aorta with an aberrant pulmonary artery there is considerable indecision. There are at present no adequate criteria and no suitable nomenclature to settle this question. Identical anomalies have been reported variously as persistent truncus arteriosus communis, truncus solitarius aorticus or atresia of the pulmonary artery. Some clarification of these anomalies can probably be achieved by considering them with respect to the developmental defect of the pulmonary artery. For purposes of analysis, the cases may be divided into four groups according to the sites of origin of the pulmonary vessels (fig. 4).

Group 1. Cases in which the lungs are supplied by arteries arising from the ascending aorta.

Group 2. Cases in which the lungs are supplied by arteries arising from the arch of the aorta.

Group 3. Cases in which the lungs are supplied by arteries arising from the descending aorta.

Group 4. Cases in which the lungs are supplied by arteries having other anomalous origins.

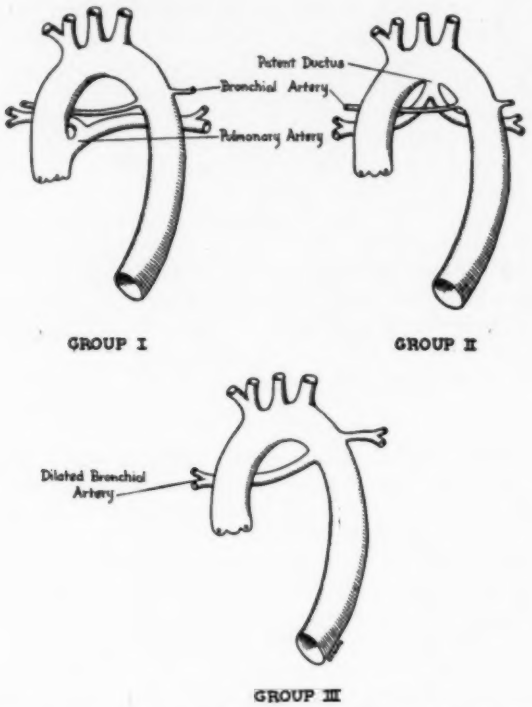

Fig. 4.—*Group 1:* The otherwise normal pulmonary artery arises from the ascending aorta (persistent truncus arteriosus communis). *Group 2:* The lungs are supplied by an artery arising from the aortic arch (absence of the pulmonary artery with persistent ductus arteriosus). *Group 3:* The lungs are supplied by arteries arising from the descending aorta (absence of the pulmonary artery with hypertrophied bronchial arteries). Notice that in groups 1 and 2 there are two sets of arteries entering the hili of the lungs, while in group 3 there is only one, the bronchial arteries. *Group 4* (not shown): a heterogeneous group similar to group 3 except that the lungs are supplied by various anomalous vessels.

Group 1: These cases present little difficulty, as they are generally accepted as exemplifying persistent truncus arteriosus communis. The arteries supplying the lungs are normal pulmonary arteries derived

from the sixth arch. A lack of development of the aorticopulmonary septum has merely failed to separate the root of the pulmonary artery from the aorta, so that both vessels arise from a common trunk, the primitive truncus arteriosus.

Group 2: These cases have usually been reported as instances of persistent truncus arteriosus communis (Graham and Montgomery,[3] Hunter,[4] Popjak[5] and others), but we believe that this is an incorrect designation. The artery supplying the lungs is actually a persistent ductus arteriosus, while the true pulmonary artery is lacking. This results from an absence or an early involution of the ventral roots of the sixth arch (the true pulmonary artery), with the left dorsal root of the sixth arch (the ductus arteriosus) maintaining continuity with the pulmonary plexus and persisting as the sole arterial supply to the lungs. To consider this vessel arising from the arch of the aorta a true pulmonary artery, as has been suggested by some, would require two improbabilities: First, it could result from a failure of the aorticopulmonary septum, which is unlikely, as the cranial extent of this septum is at the junction of the embryonic fourth and sixth aortic arches, which is proximal to the adult aortic arch. A complete failure of the septum would thus result in a pulmonary artery arising from the upper end of the ascending aorta, and not from the arch. Second, it would require that a vessel arising from the sixth arch be transposed along the aorta cephalad to the origins of other vessels (innominate and common carotid arteries) which develop from the third and fourth arches. It is improbable that such a transposition of the primitive aortic arches could occur. Hülse[6] stated that a true pulmonary artery must arise proximal to the innominate artery, and this seems to be a sound interpretation.

In some cases there may be more than one vessel arising from the concavity of the arch and supplying the lungs, and this could easily result from an absorption of the short trunk of the ductus arteriosus so that its branches would arise directly from the aorta. Another possibility that has been suggested is that these multiple vessels may represent migrated bronchial arteries. This could readily be determined, if it is a fact at all, by a careful examination of the hili of the lungs. If there is only one set of arteries entering the hili of the lungs, in close association with the bronchi on their posterior surfaces, then these would be bronchial arteries and the conception of misplaced bronchial arteries arising from the aortic arch would

3. Graham, S., and Montgomery, G. L.: J. Tech. Methods **18**:97, 1938.
4. Hunter, O. B., Jr.: Arch. Path. **37**:328, 1944.
5. Popjak, G.: J. Path. & Bact. **54**:67, 1942.
6. Hülse, W.: Virchows Arch. f. path. Anat. **225**:16, 1918.

have to be accepted. However, if two sets of vessels are found, then one would be the normal bronchial arteries and the other would represent the branches of the ductus arteriosus.

Group 3 is represented by our case and consists of hyperthrophied bronchial arteries supplying the lungs in the absence of any form of the pulmonary artery. This results from an early involution or an absence of the entire sixth aortic arch. The pulmonary plexus then maintains its original communication with the ventral branches of the dorsal aorta, which probably give rise to the hypertrophied bronchial arteries. That this anomaly must result from an absence of the sixth arch rather than from a lack of development of the aorticopulmonary septum seems obvious. As stated in a foregoing paragraph, even a complete failure of development of the septum would result in otherwise normal pulmonary arteries arising from the ascending aorta. It could in no way explain how arteries could originate from the descending aorta or from the arch of the aorta, nor could it explain absence of the pulmonary arteries.

Group 4 comprises a heterogeneous collection of rare types in which the arteries supplying the lungs arise from vessels not ordinarily associated with the pulmonary circulation. This includes cases in which the arteries arise from such vessels as the subclavian, intercostal, esophageal, phrenic, common carotid or inferior thyroid arteries[7] or from the lower thoracic or the abdominal aorta or the celiac or the superior mesenteric arteries.[8] A detailed discussion of their embryonal formation will not be attempted here, as each of these defects deserves individual consideration, and one who is interested will profit by a study of the separate case reports. However, in general, these anomalies may be considered as variations of the fundamental developmental defects described in groups 2 and 3. Those cases in which branches from the lower thoracic or the abdominal aorta are concerned are similar to those of group 3, the only difference being that the connections of the pulmonary plexus and the dorsal aorta are maintained through ventral branches lower down in the thoracic or the abdominal region of the aorta. In the other cases

7. (*a*) Abbott, M. E.: Congenital Heart Disease, in Osler, W., and McCrea, T.: Modern Medicine, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 612; Congenital Heart Disease, in Nelson's Loose Leaf Living Medicine, New York, Thos. Nelson & Sons, 1931, vol. 4, p. 207; Atlas of Congenital Heart Disease, New York, American Heart Association, 1936. (*b*) Wheeler, D., and Abbott, M. E.: Canad. M. A. J. **19**:297, 1928. (*c*) Blount, R. F., and Poth, E. J.: To be published; abstracted, Anat. Rec. **91**:5, 1945. (*d*) McCotter, R. E.: ibid. **4**:291, 1910. (*e*) Batts, M., Jr.: J. Thoracic Surg. **8**:565, 1939. (*f*) Park, E. A.: Proc. New York Path. Soc. **12**:88, 1912. (*g*) Harris, H. A., and Lewis, I.: J. Thoracic Surg. **9**:666, 1940.

8. McCotter.[7d] Batts.[7e] Park.[7f] Harris and Lewis.[7g]

the anomalies have a more complicated origin, but their development is also based on the primary loss, either complete or partial, of the pulmonary artery.

SUGGESTED CLASSIFICATION

From the foregoing, developmental considerations a new classification may be evolved for the congenital defects resulting from anomalous origins of the pulmonary blood supply. It is believed that it will aid in the proper interpretation and recognition of some of these heretofore controversial cases. Each of the previously discussed anomalies may be classified under one of the following heads:

Persistent Truncus Arteriosus: The otherwise normal pulmonary arteries arise from the ascending aorta proximal to the origin of the innominate artery (group 1). Two sets of arteries enter the hili of the lungs, the pulmonary arteries and the bronchial arteries.

Absence of the Pulmonary Artery with Persistent Ductus Arteriosus: The lungs are supplied by the ductus arteriosus arising from the concavity of the arch of the aorta (group 2). It may arise by a single trunk or its branches may arise independently from the aorta. Two sets of arteries enter the lung hili, the bronchial arteries and the branches of the ductus arteriosus.

Absence of the Pulmonary Artery with Hypertrophied Bronchial Arteries: The bronchial arteries arise from the descending aorta (or possibly from the arch) and are considerably hypertrophied and dilated, constituting the sole arterial supply to the lungs (group 3). No other arteries enter the hili of the lungs.

Absence of the Pulmonary Artery with Anomalous Pulmonary Vessels: The lungs are supplied by arteries arising from other vessels not ordinarily associated with the pulmonary circulation (group 4). Two sets of arteries enter the hili of the lungs, the bronchial arteries and the anomalous pulmonary arteries.

Isolated cases may show a mixture of these anomalies, the lungs being supplied by different anomalous vessels on the two sides, or there may be a normal pulmonary artery on one side with an anomalous vessel on the other side.

It should also be pointed out that these same anomalies may be associated with atresia rather than absence of the pulmonary artery, and thus the same classification may be used for cases of the latter type by merely substituting the word "atresia" for "absence." The functional and clinical significance is similar in either event, though the difference in the embryonal development of the anomaly should be kept in mind.

The term "absence of the pulmonary artery" was selected to identify these cases not only because it accurately defines both the anatomic lesion and the underlying developmental defect but also

because the terms in present use are inadequate to differentiate these cases. Truncus solitarius aorticus would partially describe the anatomic defect but would fail to differentiate between absence and atresia of the pulmonary artery. Stenosis or atresia of the pulmonary artery cannot, of course, be correctly applied in the cases in which there is an absence of the artery. The designation "persistent truncus arteriosus" has been used to include these cases, but we believe that it is not only incorrect but that its continued use hinders the proper understanding of these defects.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of the various cases of absence of the pulmonary artery involves chiefly their differentiation from other cases in which there is only a single arterial trunk. Their differentiation from cases of atresia depends on whether or not an atretic remnant of the pulmonary artery is present, and a careful dissection must be made to rule out this possibility. Atresia of the aorta with the pulmonary artery remaining as the solitary arterial trunk presents what is sometimes a confusing picture, but if carefully studied it is not likely to be mistaken for absence of the pulmonary artery. The only difficulty arises in distinguishing absence of the pulmonary artery from persistent truncus arteriosus communis, largely because cases of absence of the pulmonary artery have been previously presented under the latter diagnosis. Once the concept of absence of the pulmonary artery is appreciated, there is little difficulty in differentiating the two defects.

There is some disagreement in the present literature as to the correct diagnosis of persistent truncus arteriosus communis. Abbott [7a] in 1931 classified 23 cases as instances of this anomaly in her review of 1,000 cases of congenital heart disease, but Humphreys [9] in 1932 accepted only 12 cases and added another of her own. In 1942 Lev and Saphir [10] collected 12 additional cases, and since then 5 others have been reported by Doerr,[11] Van Brown,[12] Marshall,[13] Hunter [4] and Webb,[14] making a total of 30 cases according to the present standards of diagnosis. On the other hand, Shapiro [15] in 1930 found only 2 anomalies described in the literature that he would accept as true examples of persistent truncus arteriosus communis. Humphrey's

9. Humphreys, E. M.: Arch. Path. **14**:671, 1932.
10. Lev, M., and Saphir, O.: J. Pediat. **20**:74, 1942.
11. Doerr, W.: Virchows Arch. f. path. Anat. **310**:304, 1943.
12. Van Brown, D.: J. Tech. Methods **22**:101, 1942.
13. Marshall, R.: Brit. Heart J. **5**:194, 1943.
14. Webb, A. C.: Arch. Path. **42**:427, 1946.
15. Shapiro, P. F.: Arch. Path. **10**:671, 1930.

report contained a thorough review of the subject, and her work has received wide acceptance. She attempted to clarify the situation by establishing definite diagnostic criteria. The principal criteria which she evolved were the presence of a single large arterial trunk which shows the combined features of the aorta and the pulmonary artery, the trunk preferably showing four semilunar valve cusps. Secondary features noted were dextroposition of the trunk, in the "rider" position above an interventricular septal defect, and certain modifications of the crista supraventricularis and of the mitral and tricuspid leaflets. She described as "partial" types (partial defect of the aorticopulmonary septum) those in which there is a main pulmonary trunk arising from the ascending aorta and dividing into right and left pulmonary branches, and as "complete" types those in which the pulmonary trunk is missing and right and left pulmonary arteries arise independently from the aorta. Included among the "complete" types were those in which these vessels arise from the arch or from the descending aorta.

As previously discussed, we believed that cases of the latter types in which the lungs are supplied by the ductus arteriosus (from the arch) or by bronchial arteries (from the descending aorta) should be classified as cases of absence of the pulmonary artery. The absence of the sixth aortic arch is the fundamental and primary defect in these instances, occurring before the fourth week of embryonal development. Without the development of the sixth arch the stimulus or the nidus for development of the aorticopulmonary septum (fourth and fifth weeks) is lacking. Therefore, the designation "absence of the pulmonary artery" indicates the fundamental defect which is responsible for the final structure of the heart, while the use of the term "persistent truncus arteriosus communis" merely describes the secondary defect, the failure of development of the aorticopulmonary septum. It may be argued that the single trunk does represent persistence of the undivided primitive truncus arteriosus. This may be true, but in the final anomaly which we see at the autopsy table, this single trunk represents anatomically nothing more than the aorta. It can hardly be considered a common trunk of the aorta and the pulmonary artery when the pulmonary artery does not exist. Therefore, we suggest that an additional essential criterion for the diagnosis of persistent truncus arteriosus communis is that the pulmonary artery or arteries arise from the ascending aorta proximal to the point of origin of the innominate artery.

There is an interesting and challenging question concerning the number of semilunar cusps present in the valves of the single arterial trunks. It is admitted that with failure of the aorticopulmonary septum to divide the common truncus arteriosus, its four distal bulbar swellings

should give rise to a valve containing four semilunar cusps. Consequently all cases of persistent truncus arteriosus communis should show four cusps, but in less than half of the reported cases has this been true. An attempted explanation of this apparent paradox is that an abnormal number of semilunar cusps is occasionally found in even normal hearts and that the cases of common arterial trunk displaying only three valve cusps could represent a coincidental variant. However, this explanation seems wanting, especially when it is observed that the incidence of an abnormal number of valve cusps among all types of congenital heart disease is less than 5 per cent [7a]; yet the incidence of three-cusped valves in the reported cases of persistent truncus arteriosus communis is greater than 50 per cent. This in an interesting question, and one that if answered might shed considerable light on the development of congenital cardiac anomalies. It is interesting to note that of the cases of single arterial trunks showing four valve cusps reported, all but 1 belong to the type that we have designated group 1 (persistent truncus arteriosus communis), and none have been found in our group 3 (absence of the pulmonary artery with hypertrophy of the bronchial arteries).

In addition to the embryologic basis for separating the cases of absence of the pulmonary artery from those of persistent truncus arteriosus communis, there is an interesting, if somewhat surprising, clinical correlation between the two. In the 29 cases of persistent truncus arteriosus communis the average age of survival was less than two months (excluding two of Humphrey's "possible cases" in which the patients lived 16 and 25 years), whereas in the 7 cases of absence of the pulmonary artery with hypertrophied bronchial arteries the average age of survival was more than eleven years. Thus, persistent truncus arteriosus is more likely to arouse interest at the autopsy table, while absence of the pulmonary artery may assume more clinical importance.

ABSENCE OF THE PULMONARY ARTERY WITH HYPERTROPHIED BRONCHIAL ARTERIES

Our case is an example of absence of the pulmonary artery with compensatory hypertrophy and dilatation of the bronchial arteries. A review of the literature reveals that 6 similar cases have been reported (although under different diagnoses), 1 each by Hülse,[6] Zimmerman,[16] Finley,[17] Miller and Lyon,[18] Greenspon and Leaman [19] and Solis-

16. Zimmerman, H. M.: Am. J. Path. **3**:617, 1927.
17. Finley, K. H.: Am. J. Path. **6**:317, 1930.
18. Miller, M. K., and Lyon, M. W., Jr.: Am. Heart J. **7**:106, 1931.
19. Greenspon, S., and Leaman, W. G., Jr.: Internat. Clin. **4**:208, 1939.

Cohen and associates.[20] The latter 2 cases were reported as instances of complete atresia and atresia of the pulmonary artery, respectively, although no remnant of the pulmonary artery was present. If no trace of the artery is seen, the term "atresia" is incorrect, for atresia means closure of a normal opening or channel rather than absence of a structure. Furthermore, the term "complete atresia" is redundant, for atresia is actually complete stenosis. The other cases were reported as instances of persistent truncus arteriosus. Such a diagnosis would identify the single trunk as the common stem of the aorta and the pulmonary artery when actually there is no pulmonary artery. It would indicate that the fundamental embryonal fault was a failure of development of the aorticopulmonary septum, but, as already mentioned, this could not produce the lesion in question, and furthermore it hardly seems logical to describe a failure of a septum between two vessels when one of those vessels does not exist.

If the fundamental defect in these cases is considered to be an absence or an early involution of the primitive sixth aortic arch, then the complete picture can be readily explained. With the absence of the sixth arch, the pulmonary artery fails to be established and the pulmonary plexus maintains the parts by which it communicates with the ventral branches of the dorsal aorta, which become the bronchial arteries. The subsequent increase in the volume of blood flowing through these vessels produces compensatory hypertrophy and dilatation, which enable them to supply sufficient blood for aeration of the lungs. At the base of the heart the abnormal flow of blood streaming from both ventricles into the aorta prevents the closing of the basal or membranous portion of the interventricular septum and is also probably responsible for the incomplete rotation or detorsion that leads to the partial dextroposition of the aorta so that the latter is in the "rider" position. The dilatation of the root of the aorta naturally follows its increased quantity of blood, and the hypertrophy of the ventricles is a result of the cardiac embarrassment produced by the abnormal circulation. Thus these cases may be classified as absence of the pulmonary artery with compensatory dilatation and hypertrophy of the bronchial arteries, this designation giving both an accurate anatomic description and a clear indication of the underlying embryonal process leading to the development of the anomaly.

It is amazing how efficiently the bronchial arteries are able to take over in the absence of the pulmonary artery. As stated before, the average age of the 7 patients in this group was over 11 years, 3 of them reaching adulthood. This efficient bronchial substitution

20. Solis-Cohen, M.; Zaslow, J., and Rolnick, M. H.: Am. Heart J **28**:115, 1944.

is also seen to a striking degree in cases of atresia of the pulmonary artery, which functionally are similar to cases of absence of the pulmonary arteries. Christeller [21] reported 5 cases in which the patients lived from 16 to 37 years. Bach [22] recorded 1 case in which the age of 30 was attained, and East and Barnard [23] cited 2 cases in which the patients reached the ages of 20 and 33, and neither of these patients died of their cardiac anomalies.

There are two mechanisms whereby this compensatory function of the bronchial arteries may be derived, dependent on the stage of development at which the lesion of the pulmonary artery occurs. In the cases of atresia, in which the pulmonary artery has once been established, the bronchial arteries probably take over by the process of increasing their anastomotic channels within the lung. Although ordinarily no anastomosis is considered to exist between the pulmonary and bronchial circulations, Miller [24] has demonstrated by a series of intravascular injections that an indirect anastomosis is present through their common venous capillary plexus. That this is capable of developing into a free communication is evidenced by the cases cited. On the other hand, in cases of primary failure of the sixth arch, in which the pulmonary artery has never formed, it is probable that the independently developing pulmonary plexus maintains its connection with the ventral branches of the dorsal aorta, as mentioned before, and in this way the bronchial arteries are developed from the very beginning into efficient pulmonary vessels.

CLINICAL DIAGNOSIS

Although it is perhaps not possible to determine clinically the exact type of anomaly that exists in these cases, it may be possible to ascertain that one is dealing with either absence or atresia of the pulmonary artery with abnormal blood supply to the lungs. The general clinical picture may be similar to the well known tetralogy of Fallot except that there may be no murmurs. One may expect the usual stigmas of congenital heart disease, such as cyanosis, clubbing of the fingers and toes and polycythemia, but these signs are often not as marked as in the tetralogy, for the hypertrophied bronchial arteries function more efficiently than do the stenosed pulmonary arteries. It is also well to keep in mind that some of these patients may not present any symptoms of cardiac disease for a number of years. The electrocardiogram should show a right ventricular pre-

21. Christeller, E.: Virchows Arch. f. path. Anat. **223**:40, 1917.

22. Bach, F.: Lancet **1**:1009, 1928.

23. East, T., and Barnard, W. G.: Lancet **1**:834, 1938.

24. Miller, W. S.: The Lung, Springfield, Ill., Charles C Thomas, Publisher, 1937.

ponderance, and the roentgenogram will usually show the typical "coeur en sabot" outline of the heart. Danelius [25] reported a case in which a review of the roentgenograms after autopsy showed absence of the hilar shadow, and he expressed the belief that if this had been noticed and its significance appreciated, a correct antemortem diagnosis could have been made. He reviewed previously reported cases and found the same sign in many of them, suggesting that absence of the hilar shadow may be of some diagnostic importance in cases of absence or atresia of the pulmonary artery with anomalous pulmonary blood supply. However, our case failed to show this sign. Apparently it may be of positive value if present, but of no negative value if not present.

Thus, if these anomalies are kept in mind, a presumptive clinical diagnosis may be made in many of these cases. Knowledge of this would of course be of particular value to the surgeon contemplating intrathoracic correction of a defect, so that he might be able to avoid damaging any abnormal vessels encountered which might later prove to be the only ones supplying blood to the lungs or to one or more lobes of the lungs. At least two such unfortunate accidents that resulted in operative deaths have been reported.[26]

SUMMARY

Congenital cardiac anomalies involving a single aortic trunk with an abnormal site of origin of the pulmonary artery are discussed on the basis of their embryonal development and with particular reference to their recognition.

A case of absence of the pulmonary artery in which the lungs were supplied solely by hypertrophied bronchial arteries is presented. A review of the literature reveals that 6 other cases of this type have been reported. However, they were reported under various other diagnostic headings because of the fact that there had never been an adequate classification of these cases.

A new classification for this group of cases is presented which places emphasis on the maldevelopment of the pulmonary artery as the fundamental lesion in producing the final anatomic defect. It is felt that this suggested classification will help to clarify the interpretation and diagnosis of these cases.

Congenital cardiac anomalies in which there is a single arterial trunk and an abnormal site of origin of the arteries supplying the lungs may be satisfactorily classified as follows:

1. Persistent truncus arteriosus communis (incomplete development of the aorticopulmonary septum).

25. Danelius, G.: Am. J. Roentgenol. **47**:870, 1942.
26. Blount and Poth.[7e] Harris and Lewis.[7g]

2. Absence of the pulmonary artery with persistent ductus arteriosus (absence of the ventral root of the sixth arch with persistence of the left dorsal root).
3. Absence of the pulmonary artery with hypertrophied bronchial arteries (absence of entire sixth arch).
4. Absence of the pulmonary arteries with anomalous pulmonary vessels (absence of entire sixth arch).

Atresia of the pulmonary artery is similar to absence of the artery except for the mechanism of its formation, and the classification presented may be equally well applied to cases of this condition.

It is suggested that an additional requirement for the diagnosis of persistent truncus arteriosus communis is that the pulmonary arteries arise from the common trunk proximal to the origin of the innominate artery.

The value of adequate recognition of these cases is discussed with respect not only to their further study but also to the application of modern methods of surgical treatment.

RADIORESISTANT CELLS IN CERTAIN RADIOSENSITIVE TISSUES OF SWINE EXPOSED TO ATOMIC BOMB RADIATION

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THAT the threshold of tolerance to total body–penetrating ionizing radiation varies among the several species of plant and animal life is well known. In addition to species variations in radiosensitivity there are individual variations, usually of smaller magnitude, among members of the same species. However, it is interesting that in mammals as a class specific tissues bear a fairly constant radiosensitivity relationship to one another.

Irradiation of the whole body affords an effective means for study of the radiosensitivity differences of the various tissues of a living animal. However, two important filtration factors must be considered when one is calculating the dose of total body irradiation that any particular tissue receives. The lack of uniform density in the body tissues introduces the greatest single variable, but also of importance is the thickness of the animal which, owing to the shielding effect of interposed organs, may lead to errors in the calculation of the dose delivered to distal tissues. Because of the amount and the penetrating quality of the radiations, the use of atomic energy as the source of total body irradiation tends to minimize, but probably does not entirely eliminate, the effect of differences due to specific density of the tissue and body thickness of the organism.

One advantage in studying swine is that one is able to reproduce the differences in tissue density and body thickness variables which are present in man. In addition, swine are believed to be in roughly the same sensitivity range as man. For these reasons, among others, they were chosen as test animals for the Bikini atomic bomb trials in 1946.[1]

The principle of total body irradiation is a concept not generally familiar to the medical profession, but is one which takes on added significance as man advances in the atomic age. Judicious therapeutic doses of ionizing radiation localized on a tumor destroy the tumor

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From the Naval Medical Research Institute, National Naval Medical Center.

1. Draeger, R. H., and Warren, S.: U. S. Nav. M. Bull. **47**:219, 1947. Tullis, J. L., and Warren, S.: J. A. M. A. **134**: 1155, 1947.

without marked or lasting effect on the host in general. Yet it is known that with 1,000 kilovolt roentgen rays, at 1 meter distance from the source 600 roentgens (r), measured in air delivered at the rate of 30 r per minute to both lateral aspects, or something more than 1,200 r measured in air delivered to one lateral aspect, is the absolute lethal dose for swine.[2] Although such comparatively small doses delivered in a short period have a lethal effect on the swine, many cells and organs show no morphologic evidence of injury. The radioresistant tissues are usually highly differentiated and include nerve, muscle, bone and cartilage.

The tissues of the Bikini swine which showed the greatest morphologic changes were the lymphoid organs—including lymph nodes, the spleen, the thymus, the tonsils and lymphoid aggregations in the bowel wall, as well as lymphocytes in the peripheral blood stream—the bone marrow, the intestinal epithelium and the gonads.[3] The comments in this report are limited to observations concerning the morphologic changes noted in these radiosensitive tissues.

LYMPHOID CELLS AND TISSUES

Lymphocytes are probably the most radiosensitive cells in the body. Following irradiation there is a prompt reduction in circulating lymphocytes and in the lymphocyte population of the lymphoid organs. The lymphocytes undergo rapid lysis in some cases, but in others they undergo a more leisurely degeneration and can be spotted as free or as phagocytosed nuclear debris. In lymph nodules destruction of lymphocytes serves to demonstrate by contrast the survival of the reticular cells (fig. 1). Recent observations on animals exposed to external and internal ionizing radiations from atomic, radioactive isotopes and roentgen ray sources have established the fact that reticular cells are relatively radioresistant as judged by morphologic standards.[4]

However, in lymph nodes and the spleen the macrophages are not altered structurally, and functionally they appear to be hyperactive. Erythrophagocytosis in these tissues occurs with greater than normal frequency. This should not imply that stimulation of the macrophages has occurred, but simply that they are keeping abreast of their increased work load, namely, the phagocytosis of injured red blood cells, degenerating white blood cells and blood pigment. Evidence of erythrophagocytosis is found in most of the spleens and lymph nodes examined of those animals which died the second day or later after exposure (fig. 2).

2. Tullis, J. L.; Tessmer, C. F.; Cronkite, E. P., and Chambers, F. W., Jr.: Radiology **52**:396, 1949.

3. Tullis, J. L.: Am. J. Path., to be published.

4. (*a*) Bloom, W.: Histopathology of Irradiation from External and Internal Sources, New York, McGraw-Hill Book Company, Inc., 1948. (*b*) Tullis.[3]

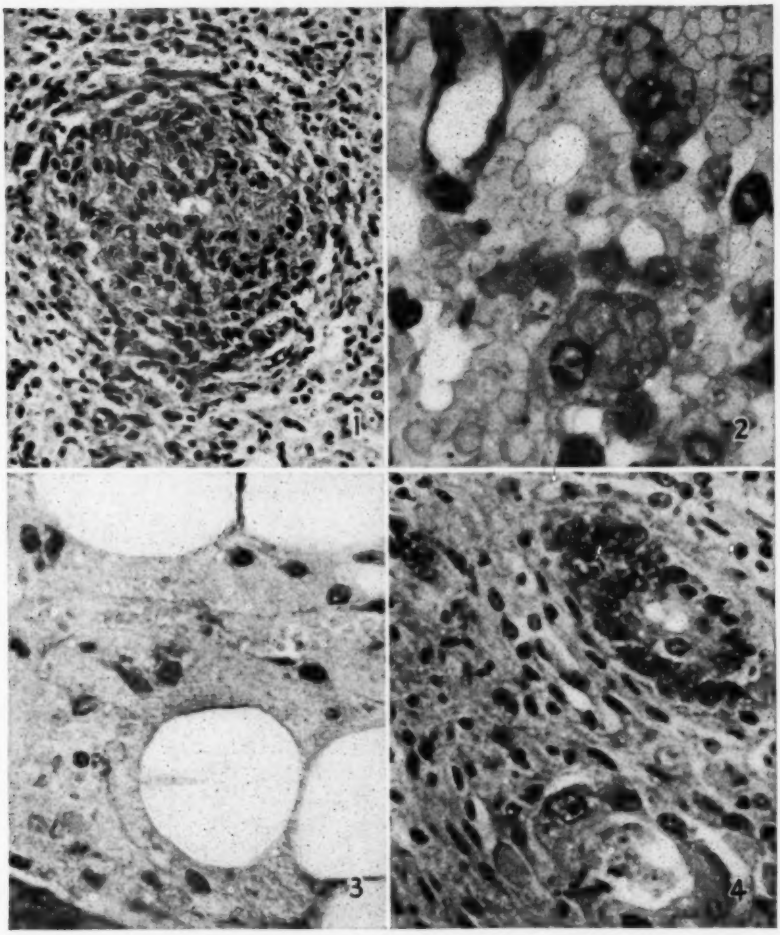


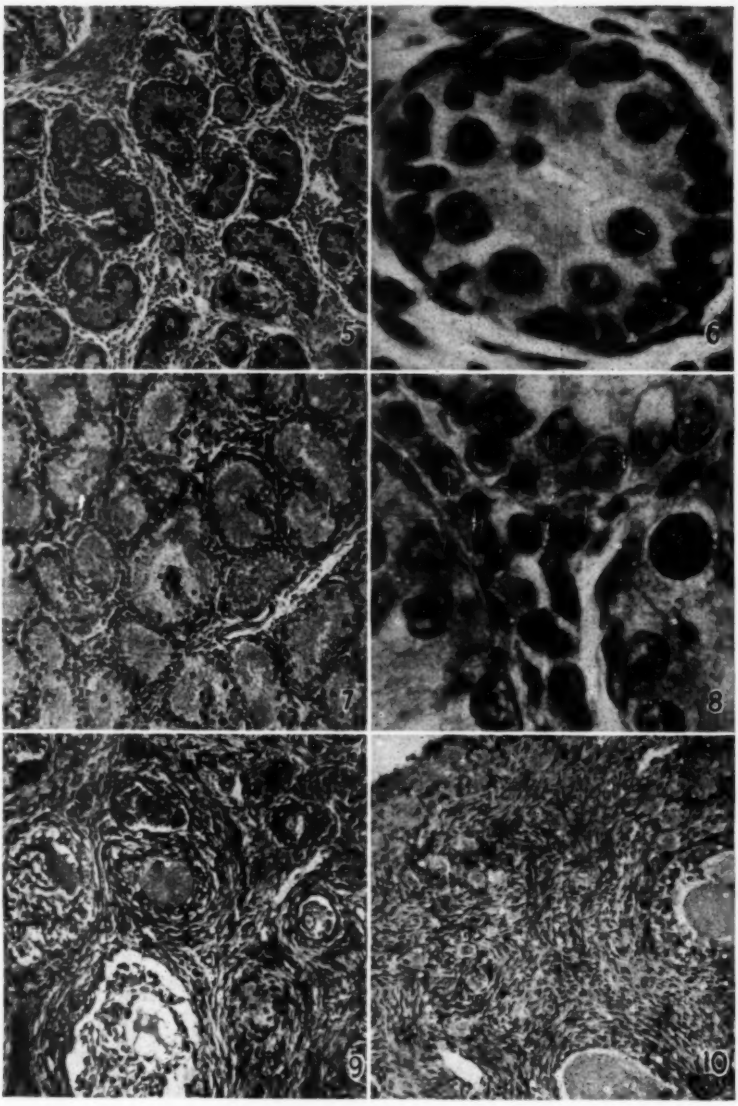
Fig. 1.—Lymph node from pig 265 six days after irradiation. Most of the lymphocytes in this nodule have been destroyed leaving numerous, apparently normal, reticular cells exposed to view. × 300.

The swine mentioned in this and subsequent legends received over 1,000 rem total body irradiation during Test Baker (underwater explosion) at Bikini. The abbreviation rem stands for the roentgen-equivalent man-unit of energy absorbed in tissue biologically equivalent in man to 1 r of roentgen or gamma radiation.

Fig. 2.—Lymph node from pig 393 eleven days after irradiation. Two phagocytes containing red blood cells and blood pigment granules are seen. × 1,350.

Fig. 3.—Bone marrow from pig 265 six days after irradiation. Reticular cells in an amorphous homogeneous matrix; fat cells and erythrocytes outnumber other cellular elements. × 645.

Fig. 4.—Small intestine from pig 419 five days after irradiation. The cells lining the glands show marked variation in size, shape and distribution of chromatin. Many of the cells in the lamina propria are pyknotic, while others have completely disappeared. × 400.



FIGURES 5-10

(See legends on opposite page)

BONE MARROW

In the bone marrow the blast cells of both the red and the white cell series are very radiosensitive while the more mature cells are less radiosensitive. However, even after doses of total body irradiation sufficient to destroy nearly all the maturing cells in the marrow, the reticular cells remain intact (fig. 3). Investigators are thus faced with an interesting phenomenon in which blast cells and maturing and mature cells are destroyed, leaving intact only the elementary stem cells, as has been described by others.[5]

EPITHELIUM OF BOWEL

The intestinal epithelium is radiosensitive and reacts in a variety of ways. Complete destruction of the epithelium with ulceration of the muscularis mucosae may occur at random, chiefly in the large and less frequently in the small bowel. The reason for the localization of the ulcers is not apparent, although the presence of lymphoid aggregations in the basal lamina propria may possibly be a precipitating factor. There may be no remnants of lymphoid elements, and no unusual feature may be observed which would account for the localization of the ulcers. The margins of the necrotic tissue are sharply demarcated, often with one row of partially damaged glands forming the boundary between ulcerated and uninvolved areas. The cells of the marginal glands and glands elsewhere with minimal involvement show considerable variation in size, shape, amount and distribution

5. Shouse, S. S.; Warren, S. L., and Whipple, G. H.: J. Exper. Med. **53**:421, 1931. Bloom, M. A., and Bloom, W.: J. Lab. & Clin. Med. **32**:653, 1947.

EXPLANATION OF FIGS. 5-10

Fig. 5.—Testis from control pig 250. Numerous spermatogonia are observed in the tubules. Spermatocytes and lumens have not yet formed in the tubules. × 150.

Fig. 6.—Testis from control pig 250. The distribution and relative numbers of spermatogonia and indifferent cells are seen. × 300.

The swine mentioned in these legends, except pig 250 (control), received over 1,000 rem total body irradiation during Test Baker (underwater explosion) at Bikini.

Fig. 7.—Testis from pig 330 thirteen days after irradiation. Most spermatogonia and all but a few spermatocytes have been destroyed. The larger size of the tubules, the beginning of the formation of lumens and the presence of spermatocytes indicate that pig 330 was two to three weeks older than pig 265. Compare with figure 4. × 150.

Fig. 8.—Testis from pig 330. One spermatogonium is seen in this portion of three tubules, indicating extensive destruction of these cells. The indifferent cells are unharmed. The amorphous material in the central portion of the tubules is vacuolated. × 300.

Fig. 9.—Ovary from pig 364 seven days after irradiation. The ova and the surrounding follicular cells are vacuolated. × 150.

Fig. 10.—Ovary from pig 402 thirteen days after irradiation. The primordial ova and the ovarian stroma appear normal. × 150.

of chromatin in the nuclei (fig. 4). The epithelium in neighboring glands may have large vacuolated nuclei or pyknotic nuclei. Again there is no apparent local determining factor to account for the type of reaction observed.

It is noteworthy that the lymphocytes in the lamina propria are greatly diminished, but that the fibrocytes and plasmacytes are apparently uninjured.

GONADS

The same pattern of response observed in the lymphoid organs and the bone marrow is also manifest in the testis. The Bikini swine were 3 to 3½ months of age at the time of the experiment, and the males had just begun to mature sexually.

On histologic examination it is observed that the lumens of the tubules are beginning to form. Many stem or so-called "indifferent" cells, a few spermatogonia and, in some areas, a few spermatocytes are present (figs. 5 and 6). No fully formed sperm is observed. Within five days after lethal total body irradiation most of the spermatogonia and spermatocytes disappear. The cytoplasm of the tubular cells and the amorphous interstitial material of the tubules become granular, stringy and vacuolated (fig. 7). On the other hand, the indifferent cells which line the tubules next to the basement membrane show no structural alterations, nor are they reduced in number (fig. 8).

In the ovary the primordial ova seem to be more resistant to irradiation than the developing ova. The latter show such changes as vacuolation of the cytoplasm of the follicular cells and lysis and fragmentation of the chromatin of the ova (fig. 9). In most cases in swine the primordial ova show no morphologic changes (fig. 10), but this evidently does not hold true for all species.[4a] The ovarian stroma is radioresistant but may become slightly edematous after total body irradiation.

COMMENT

The significance of these observations is concerned with the fact that the reticular cells of the lymphoid organs and the bone marrow, the indifferent cells of the immature testis and the primordial ova, all of which cells are the so-called stem cells of their respective highly radiosensitive organs, are comparatively radioresistant. This poses an important exception to the law of Bergonié and Tribondeau[6] (primitive cells are more sensitive to radiation than specialized cells), which should be modified to mention specifically that the stem cells are excluded in the progression of radiosensitivity postulated.

6. Bergonié, J., and Tribondeau, L.: Compt. rend. Acad. d. sc. **143**:983, 1906.

The qualities which make such cells as the reticular cells of lymphoid organs and bone marrow, fixed and circulating macrophages, and plasmacytes relatively much more radioresistant than the closely related lymphocytes are not apparent morphologically.

The purpose of this paper is to point out that there are certain radioresistant elements in the more radiosensitive organs of the body with the hope that this knowledge will cause the physiologist and the histochemist to focus their search for the mechanism of ionizing radiation injury on the metabolic and chemical differences of the radiosensitive as compared with the radioresistant elements. The great importance attached to the radioresistance of certain stem cells is concerned with recovery of the organism from radiation injury. It is apparent that if treatment during the acute phase of the injury is successful in maintaining life, there is histologic evidence that regeneration of radiosensitive cells can be accomplished by the surviving stem cells.

EFFECT OF TRIPELENNAMINE HYDROCHLORIDE ON ACUTE INFLAMMATION

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ALTHOUGH many workers [1] have attributed the sequence of events in acute inflammation to the influence of chemical substances which are released from injured tissue, such substances have not been precisely identified. In particular, much conflicting evidence exists regarding the role of histamine or an "H substance" in the acute inflammatory process.[2]

The demonstration [3] that such antagonists of histamine as diphenhydramine (benadryl® [beta dimethylaminoethyl benzhydryl ether]), tripelennamine (pyribenzamine® [N,N-dimethyl-N′-benzyl-N′-(alpha-pyridyl) ethylenediamine]) and pyranisamine (neo-antergan® [N,N-dimethyl-N′-(p-methoxybenzyl)-N′-(alpha-pyridyl) ethylenediamine]) markedly alter the response of the skin to histamine suggested their use to investigate the part played by histamine in acute inflammation.

It was postulated that if histamine caused the local vasodilatation and increased permeability of capillaries noted in inflammation, as was suggested by Lewis,[4] the administration of an antagonist of histamine such as tripelennamine would alter the process of acute aseptic inflammation.

From the Department of Pathology, Northwestern University Medical School.

1. Ebbecke, U.: Arch. f. d. ges. Physiol. **169**:1, 1917. Lewis, T., and Grant, R. T.: Heart **11**:209, 1924. Dale, H. H.: Lancet **1**:1233, 1929. Menkin, V.: Dynamics of Inflammation: An Inquiry into the Mechanism of Infectious Processes, New York, The Macmillan Company, 1940.

2. (*a*) Menkin, V.: J. Exper. Med. **64**:485, 1936; (*b*) Proc. Soc. Exper. Biol. & Med. **40**:103, 1939; (*c*) J. Exper. Med. **67**:129, 1938. (*d*) Bier, O., and Rocha e Silva, M.: Arq. Inst. biol. São Paulo **9**:109, 1938; (*e*) Compt. rend. Soc. de Med. **129**:769, 1938. (*f*) Rous, P., and Gelding, H. P.: J. Exper. Med. **51**:27, 1930. (*g*) Wayne, E. J.: Heart **16**:53, 1931. (*h*) Grant, R. T., and Jones, T. D.: ibid. **14**:336, 1927.

3. Arbesman, C. E.; Koepf, G. F., and Miller, G. F.: J. Allergy **17**:203, 1946. Yonkman, F. F.; Chess, D.; Mathieson, D., and Hanson, N.: J. Pharmacol. & Exper. Therap. **87**:122, 1945. Friedlander, S., and Feinberg, S.: J. Allergy **17**: 129, 1946.

4. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927.

MATERIALS AND METHODS

Effect of Vasodilatation.—Two groups of female albino rabbits were used. In series A, consisting of 10 rabbits, three areas of acute inflammation were induced on the ventral aspect of the ear by ten seconds' application of a metal rod, 0.9 cm. in diameter, which had been heated to 90 C. In series B, consisting of 11 rabbits, three intradermal injections of 0.02 cc. of turpentine served as the irritant. Since it was noted that the area of erythema was maximal three minutes after application of the stimulus, the erythematous areas were transilluminated, traced and measured with a planimeter at this time. The average of three measurements was used.

Shortly after the control measurements had been taken, each animal was given intravenously 4.0 mg. of tripelennamine hydrochloride[5] per kilogram of body weight. Thirty minutes later the same stimuli were applied to analogous areas on the opposite ear, and the resulting erythema was measured.

Histamine skin wheals were produced in 20 rabbits by an intradermal injection of 0.02 cc. of a 1:20,000 solution of histamine phosphate in sterile isotonic solution of sodium chloride. The injections were made in areas corresponding to those used for the procedures described in the foregoing paragraphs, before and after administration of tripelennamine hydrochloride. The resulting erythema was measured.

Effect of Permeability of Capillaries.—Inflammatory responses to burns, turpentine and histamine were produced, as previously described, on the shaved abdomens of 12 rabbits. Seven of these animals had received intravenously 4.0 mg. of tripelennamine hydrochloride per kilogram of body weight thirty minutes before the stimuli were applied, and 5 served as controls. The permeability of capillaries was estimated by the intensity of the concentration of dye three, thirty and one hundred and eighty minutes after 10 mg. of trypan blue had been injected into the marginal vein of an ear.

Rabbits 1 through 9 were normal rabbits. Rabbits 10 through 20 had been used earlier for the Friedman test, but the abdominal wounds were healed and the animals were in good health. In experiments requiring repeated injections of tripelennamine hydrochloride, at least forty-eight hours were allowed to elapse between injections. No anesthesia was used.

Microscopic sections of tissues fixed in formaldehyde solution and stained by the hematoxylin-eosin technic were made at varying intervals after the inflammatory stimulus had been applied.

EFFECT ON VASODILATATION

Burns (series A).—After the administration of tripelennamine, the areas of erythema were reduced in all animals. The reductions ranged from 25 to 78 per cent as compared with the control measurements of the burns on the opposite ear. The average reduction was 43 per cent (table 1).

Injections of Turpentine (series B).—Reduction of the erythema was noted in 7 of the 10 animals after the administration of tripelennamine. The decreases ranged form 11 to 62 per cent as compared with

5. Pyribenzamine hydrochloride,® supplied by Ciba Pharmaceutical Products, Inc., was used.

the control measurements. The average reduction was 29 per cent (table 2).

Histamine Wheals (series A and B).—Tripelennamine reduced the erythema from 19 to 85 per cent as compared with the control measurements. The average reduction was 47 per cent (table 3).

No correlation was noted between the reduction of the histamine flare and that of the erythema following each of the other stimuli.

TABLE 1.—*Areas of Erythema Following Standard Burns in Square Millimeters*

Rabbit	Before Tripelennamine	After Tripelennamine	Reduction, Per Cent
1	92	70	23
2	79	28	65
4	131	103	21
5	94	71	25
6	123	93	25
7	156	73	54
11*	132	72	46
12*	125	27	78
13*	91	57	38
14*	101	65	35
			Av. reduction 43 per cent

* This rabbit was previously used for the Friedman test.

TABLE 2.—*Areas of Erythema Following Injections of Turpentine in Square Millimeters*

Rabbit	Before Tripelennamine	After Tripelennamine	Reduction, Per Cent
5	129	90	31
6	108	96	11
7	108	106	0
8	192	107	44
10*	245	223	9
15*	318	148	53
16*	290	167	42
17*	211	158	25
18*	319	121	62
19*	356	346	3
20*	204	93	55
			Av. reduction 29 per cent

* This rabbit was previously used for the Friedman test.

These measurements were made on different days. The intensity of the erythema, as well as the area, was decreased in all animals.

EFFECT ON PERMEABILITY OF CAPILLARIES

In the studies of permeability of capillaries, no reduction of the intensity of dye concentration was noted following the administration of tripelennamine hydrochloride when burns and injections of turpentine were used as the stimuli, but the localization following injections of histamine phosphate was completely prevented (table 4).

6. Footnote deleted by the authors.

No alteration of cellular exudate was noted microscopically. It is difficult to judge vasodilatation from tissue sections.

The doses of tripelennamine hydrochloride used produced increased irritability and restlessness in the animals and, if given rapidly, caused convulsions. Although the area of ertyhema following a standard stimu-

TABLE 3.—*Areas of Erythema Following Injections of Histamine Phosphate in Square Millimeters*

Rabbit	Before Tripelennamine	After Tripelennamine	Reduction, Per Cent
1	122	18	85
2	57	10	82
3	98	64	33
4	119	97	19
5	154	35	78
6	104	70	30
7	106	84	20
8	176	47	76
9	163	112	31
10*	131	84	36
11*	130	46	65
12*	145	62	57
13*	97	60	39
14*	88	51	43
15*	122	78	35
16*	159	33	78
17*	118	65	46
18*	137	81	41
19*	170	78	53
20*	188	35	85
			Av. reduction 47 per cent

* This rabbit was previously used for the Friedman test.

TABLE 4.—*Intensity of Trypan Blue Concentration at Sites of Inflammation*

Rabbit	Administration of Tripelennamine	Concentration		
		Histamine	Burns	Turpentine
1	Yes	Negative	3 plus	
4	Yes	Negative	3 plus	1 plus
6	Yes	Negative	2 plus	Negative
7	No	1 plus	3 plus	2 plus
8	Yes	Negative	2 plus	2 plus
10*	No	2 plus	2 plus	1 plus
11*	Yes	Negative	2 plus	
14*	Yes	Negative	2 plus	
15*	No	2 plus	2 plus	2 plus
21*	No	2 plus	3 plus	

* This rabbit was previously used in the Friedman test.

lus varied from animal to animal and from day to day in the same animal, it was remarkably constant in the same animal on the same day. No difference of response was noted between the normal rabbits and those used previously for Friedman tests.

COMMENT

In these studies tripelennamine was effective in reducing the vasodilatation that followed the intradermal injection of concentrations of

histamine phosphate comparable to those occurring in inflammatory exudates. Tripelennamine's antagonism to histamine is thought to resemble that described by Wells and associates [7] for diphenhydramine (benadryl®), which is a competitive adsorption of the drug on the effector cells sensitive to histamine. Since the drug shows no atropine-like effects, it is considered to be more specific as an antagonist of histamine than diphenhydramine.[8]

Interpretation of the reduction of the erythema produced by a burn, as well as of that following the injection of a foreign substance such as turpentine, following the administration of tripelennamine requires further study. This effect might be due to stimulation of any of the vasoconstrictor mechanisms or to inhibition of the vasodilator mechanism, as well as to an action on some substance produced locally by trauma.

The failure of tripelennamine to alter the intensity of the concentration of trypan blue following burns and injections of turpentine, while completely obliterating that following injections of histamine phosphate, suggests that substances other than histamine are responsible for the increased permeability of capillaries involved in inflammation. Menkin [2a] has attributed this increased permeability to leukotaxine, and Collumbine [9] has shown recently that the action of leukotaxine is not altered by pyranisamine (neo-antergan®), an antagonist of histamine.

SUMMARY

In these experiments tripelennamine reduced the erythema and the increase in permeability of capillaries that follow the intradermal injection of concentrations of histamine comparable to those found in inflammatory exudates. The drug reduced the erythema that followed burns and injections of turpentine under similar experimental conditions, but failed to alter the increase of capillary permeability that follows the application of these irritants. No alteration of the microscopic picture of acute inflammation was noted after administration of the drug.

7. Wells, J. A.; Morris, H. C.; Bull, H. B., and Dragstedt, C. A.: J. Pharmacol. & Exper. Therap. **85**:122, 1945.

8. Sherrod, T. R.; Loew, E. R., and Schloenner, H. P.: J. Pharmacol. & Exper. Therap. **89**:247, 1947.

9. Collumbine, H.: Nature, London, **159**:841, 1947.

GLIOMA OF THE NOSE

Report of a Case of the Extranasal Type

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ALTHOUGH congenital glioma of the nose is clinically benign, it has considerable interest because of its rarity and because of the unusual location. In most of the reported cases there is a subcutaneous tumor forming an external swelling in the region of the bridge of the nose (extranasal type).[1] In a few cases the tumor has been wholly within the nasal cavity (intranasal type).[2] In other cases the tumor has been both extranasal and intranasal (mixed type).[3] Glioma of the nose must be differentiated from gliomatous encephalocele (brain hernia), which occurs in the same locations but which has a definite intracranial connection that can be traced through a defect in the bone beneath the tumor.

REPORT OF CASE

A white infant, a boy weighing 2,500 Gm., was delivered from a primipara 20 years of age after an uneventful pregnancy and labor. (Dr. Margaret Clark, of Lawrence, Kan., gave me permission to use the case.) He appeared normal except for a tumor on the left side of the bridge of the nose, which presented no unusual widening. The tumor, which was covered by intact skin, appeared to be a dome-shaped mass measuring about 12 mm. in diameter across its broad base. There had been no unusual maternal illnesses during the pregnancy. At the end of six days the tumor had not definitely increased in size but was removed for cosmetic reasons by sharp dissection, with the infant under local anesthesia. The base of the wound, which lay almost on the periosteum, was fulgurated since it was believed that all of the tumor tissue had not been removed. The preoperative impression was that the tumor was a hemangioma. There had been no recurrence eight months later, and the scar was almost unnoticeable.

The specimen measured 16 mm. in diameter and 6 mm. in thickness. It was dome shaped, and over the surface there was intact epidermis. This rather soft

From the Department of Pathology, University of Kansas School of Medicine.

1. (*a*) Schmidt, M. B.: Virchows Arch. f. path. Anat. **162**:340, 1900. (*b*) Sussenguth, L.: ibid. **195**:537, 1909 (*c*) Comninos, O.: Arch. d'opht. **31**:177, 1911. (*d*) Berblinger, W.: Centralbl. f. allg. Path. u. path. Anat. **31**:201, 1920. (*e*) Davis, E. W.: J. Neuropath. & Exper. Neurol. **1**:312, 1942. (*f*) Bratton, A. B., and Robinson, S. H. G.: J. Path. & Bact. **58**:643, 1946.

2. (*a*) Clark, J. P.: Am. J. M. Sc. **129**:769, 1905. (*b*) Schwartz, A. H., and Isaacs, H. J.: Arch. Otolaryng. **34**:838, 1941.

3. (*a*) Rocher, H. L., and Anglade: Rev. de chir. **62**:147, 1924. (*b*) Clark.[2a]

specimen cut without increased resistance, and the cut surface had a light grayish, somewhat gelatinous appearance with a small central light brown area of softening.

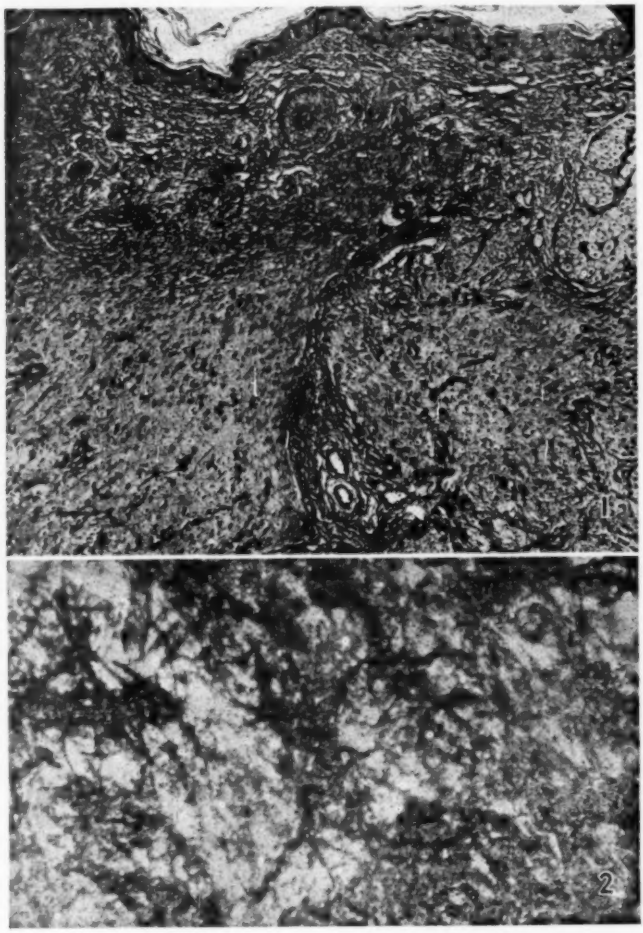

Fig. 1.—Photomicrograph of tumor showing masses of glial tissue beneath intact epidermis; phosphotungstic acid-hematoxylin; × 70.

Fig. 2.—Photomicrograph of tumor showing atypical astrocytes; Cajal's gold chloride-mercuric chloride mixture; × 400.

Histologic examination revealed in the corium a large mass of delicate fibrillar tissue extending to the margin of excision (fig. 1). There were varying numbers of capillaries and a few foci of hemorrhage. The nuclei had a fairly

uniform appearance, although a few were large and somewhat vesicular. In hematoxylin-eosin preparations the cytoplasm was indistinct except for the few multinucleated cells, which had a moderate amount of light pink cytoplasm. In sections stained with phosphotungstic acid–hematoxylin and with Cajal's gold chloride–mercuric chloride mixture, there were numerous branching cells, some of which were rather large and had coarse, elongated processes (fig. 2). In some fields these glia-like fibers were loosely arranged, while in others they formed compact masses, usually with a parallel arrangement.

Diagnosis.—Glioma of the nose, extranasal type.

COMMENT

Encephalocele (brain hernia) may occur in the same locations as nasal glioma and, moreover, may form a solid tumor with a gliomatous aspect.[4] In some of the cases the intracranial connection is narrow and may be merely a fibrous cord. In reports of 2 cases of nasal glioma, mention is made of defects in the bone beneath the tumor which were sealed over with fibrous tissue,[1c, e] so that prior existence of an intracranial connection might have been suspected. In view of these facts it is reasonable to suppose that the nasal glioma is derived from an encephalocele of embryonal life in which the part connecting it with the brain is lost through closure of the frontal bones.

Doubt has been expressed as to the neoplastic character of the glial tissue (Gutherie and Dott[5]; Browder[4b]), the inference being that the atypical astrocytes represent hyperplasia or gliosis rather than a true neoplasm. The histologic aspect is similar to that of a well differentiated astrocytoma, and the growth characteristics, i. e., failure to recur or to metastasize, do not afford a distinction between glioma and gliosis. In some cases of nasal glioma and gliomatous encephalocele the tumor has increased in size but not in others. In some cases the tumor has been removed before enough time has elapsed for growth to be detected. Certainly, the factors which Penfield[6] stated to be favorable to gliosis (circulatory impairment, death of cerebral tissue and obliteration of the subarachnoid and perivascular spaces) must exist in cases of encephalocele. Other observers[7] have compared the astrocytic tissue in cases of glioma of the nose with the cerebral glioses. Davis applied the term "nasal fibroglial heterotopia" to the finding in his case. It is surprising

4. (*a*) Fevre, M., and Huguenin, R.: Ann. d'anat. path. **13**:333, 1936. (*b*) Browder, J.: Ann. Otol., Rhin. & Laryng. **38**:395, 1929. (*c*) Rawson, J. D., and Vivoli, D.: Rev. med. latino-am. **14**:860, 1929. (*d*) Rocher and Anglade.[3a]

5. Gutherie, D., and Dott, N.: J. Laryng. & Otol. **42**:733, 1927.

6. Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2, p. 457.

7. Comninos.[1e] Rocher and Anglade.[3a]

to discover that only well differentiated glial tumors have been observed. At the present time there is insufficient evidence to abolish the use of the term "glioma of the nose."

Accurate differentiation between glioma and encephalocele of the nose requires detailed anatomic study either by adequate surgical exposure or by necropsy to determine the presence or the absence of an intracranial connection. This problem, which is well presented by Zollner,[8] has practical importance, since in some cases encephalocele has cerebrospinal fluid channels, and death has resulted from meningitis following removal of a gliomatous encephalocele.

A clinicopathologic comparison of gliomas and neuroblastic tumors of the nasal fossa has been presented by Portmann and Beillard,[9] and a similar comparison has been made by Jemmi.[10]

New and Devine [11] referred to 3 cases in which a small encephalocele appeared to be similar if not identical with glioma of the nose, but a detailed description is not presented. Reference has been made to a possible case of nasal glioma by Eggston,[12] but again a detailed description is lacking.

In my case fibrous tissue did not form an integral part of the proliferative process, while in other instances it has formed a prominent tissue element leading to the term "fibroglioma." The fibrous tissue was considered homologous with the pia mater by Schmidt. In many cases gemistocytic astrocytes and Nissl's plump cells have been described. They were not numerous in my case.

Pathologically, nasal glioma is to be differentiated from encephalocele, meningoencephalocele, ganglioneuroma, neurinoma, neurofibroma and a nerve tumor of the olfactory tract. Clinically, angioma, lipoma and dermoid cyst have to be considered.

SUMMARY

A rare congenital benign glial tumor occurring at the root of the nose is described which probably arose from ectopic brain tissue separated by an anomaly of development in early embryonic life. Although the neoplastic character of the growth is debatable, retention of the term "glioma of the nose" seems desirable.

8. Zollner, F.: Frankfurt. Ztschr. f. Path. **49**:82, 1935.
9. Portmann, G. and Beillard, P. F.: Rev. de laryng., otol., rhin. **68**:125, 1947.
10. Jemmi, C.: Oto-rino-laring. ital. **15**:149, 1947.
11. New, G. B., and Devine, K. D.: Arch. Otolaryng. **46**:163, 1947.
12. Eggston, A. A., and Wolff, D.: Histopathology of the Ear, Nose and Throat, Baltimore, Williams & Wilkins Company, 1947, p. 774.

Case Reports

CARCINOID OF THE RECTUM

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CARCINOID originating in the rectum appears to be quite rare, since only 14 cases were found described in the available literature. Furthermore, in reviewing the characteristics of the tumor in these cases, it was discovered that in only 2 cases did it have an affinity for the silver stain. In addition, metastases were noted in 2 other cases.

Since a recently observed example of carcinoid of the rectum showed both argentaffinity and a metastasis, it was considered of sufficient interest to report.

R. I. W., a 57 year old white man, entered the hospital with signs and symptoms suggestive of a recurrence of a ruptured intervertebral disk that had been treated surgically four years previously. On physical examination a 3 by 5 cm., firm, hard tumor, resting on a broad base, was discovered 5 cm. within the rectum on the left wall. There was a history of five bouts of mild and painless rectal bleeding six months before.

It was considered that the tumor was of primary concern, and conservative treatment of the back pain produced satisfactory results during the subsequent investigations. Roentgen studies of the chest and the gastrointestinal tract revealed no abnormalities. The tumor was not demonstrated in the roentgenograms. Serologic tests gave negative results, and the blood and urine were normal.

Microscopic examination of a specimen removed from the edge of the tumor showed rectal mucosa abruptly terminating in dense fibrous tissue infiltrated by nests of small round cells of fairly uniform character with solid, dark nuclei. Further specimens were requested. A second specimen consisted of twelve bits of tissue. Sections revealed normal mucosa in which there were some areas of glandular hyperplasia with piling-up of the cells into several layers. The basement membranes, as seen, appeared intact. In the area of the tunica propria there were diffuse to densely packed islands of cells as described. The muscularis could be seen to be invaded by these cells.

A one stage abdominoperineal resection was performed. The pathologic report of the surgical specimens follows.

"The specimens consist of an anorectal piece of bowel, 20 cm. long, and a 36 cm. length of sigmoid bowel.

"Lower piece: 2 cm. from the anorectal junction there is a round, firm, pseudolobulated, yellow tumor 2.6 cm. in diameter. It rests on a base 2 cm. in diameter. The mucosa runs up to the side of the tumor and stops. On cut section the

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tumor is firm, yellow and composed of various-sized lobules. It is dense in consistency and attached to the submucosal tissues. No infiltration is detected grossly. At the upper end of the piece of bowel is an elongated hard lymph node, 3.5 by 1 cm., within the fatty tissue. On section this node is morphologically identical with the tumor. The upper piece of bowel reveals no abnormality.

"Microscopic sections (hematoxylin and eosin) reveal portions of the surface to be covered with an atrophic layer of rectal mucous membrane. At one point, however, there are changes to hyperplastic proliferation. The submucosa is heavily infiltrated with plasmacytes, lymphocytes, eosinophils and tumor cells. In the submucosa and muscularis there is a marked desmoplastic reaction with a heavy interlacing network of fibrous connective tissue containing tumor cells. These

Argentaffin carcinoid of the rectum.

cells are growing in cords, and form sheets and columns in their stroma. The cells have medium to abundant cytoplasm containing occasional fine granules and many vacuoles of varying sizes. The nuclei are of varying sizes and shapes but are generally large and irregularly oval in outline. They are irregularly granular but are usually deeply so. Mitotic figures are present in small numbers.

"With Masson's silver stain, the bulk of the tumor cells do not accept the silver, and it is observed that the cytoplasm of these cells is not granular. Argentaffin cells occur in clumps and are of larger than average size. The argentaffin granules are fine and are usually unipolar, but may be bipolar, and are occasionally diffusely distributed throughout the cytoplasm."

Early convalescence of the patient was uneventful, with exercises started the fourth day. It was difficult to keep him out of bed. On the twenty-second postoperative day, after taking a bath, the patient was seized with painless dyspnea,

followed by cyanosis, collapse and death within a few minutes. Autopsy revealed massive emboli in both pulmonary arteries. The pelvic region had a dry, subsiding fibrinous peritonitis with some retroperitoneal adenopathy and a number of thrombosed small veins. No metastases were found.

COMMENT

Several different theories have been advanced for the origin of carcinoid of the intestine. The recent literature appears generally in agreement that the cells of origin are within the depths of the crypts of Lieberkühn.[1] The argentaffinity of the Kultschitzky cells, as well as their chemical, morphologic and developmental similarities to carcinoid cells are provocative.[2]

Argentaffin basigranular cells occur throughout the gastrointestinal tract. Argentaffin carcinoids have been reported[3] occurring in all portions of the intestinal tract. The percentage of these tumors accepting the silver stain is much higher in the small bowel and appendix than in the rectum.

Ersparmer and others[1] have postulated "pre-enterochrome" and "enterochrome" states of the basigranular cells; that the staining reaction, or presence of, granules depends on the metabolic state of the cell at the moment of fixation. Either confirmation or disproof of this theory would make it appear of little profit to separate these poorly understood tumors into two classes because of the silver staining properties of a fraction of the cells in some of them.

SUMMARY

A case of an argentaffin carcinoid of the rectum is reported.

1. Cited by Stout, A. P.: Am. J. Path. **18**:993, 1942.
2. Masson, P.: Am. J. Path. **4**:181, 1928.
3. Porter, J. E., and Whelan, C. S.: Am. J. Cancer, **36**:343, 1939.

Laboratory Methods and Technical Notes

GIEMSA STAIN

AT THE April 16 meeting of the Biological Stain Commission, the Board of Trustees voted that hereafter Giemsa stain will be certified in two varieties, namely, "Giemsa stain, azure B type, for malaria and blood work" and "Giemsa stain, azure A type, for hematology and bacteriology."

The azure B type closely resembles tinctorially and spectroscopically the Grübler and Hellborn Giemsa stains of the 1930's and is the variety especially recommended to give the faintly greenish blue tint to parasite cytoplasm which contrasts well with the grayish or greenish blue background of the thick film stained at p_H 7.0. This is recommended by many malariologists for thick film work.

The azure A type gives darker red chromatin stains, grayer or more violet blue lymphocyte cytoplasm and perhaps somewhat heavier staining of micro-organisms. Its useful life is probably shorter under average tropical storage conditions. It is preferred by many American hematologists.

Notes and News

Appointments, Retirements, Etc.—Appointment of Dr. H. G. Grady as scientific director of the American Registry of Pathology has been announced by Brig. Gen. Raymond O. Dart, director of the Army Institute of Pathology. Dr. Grady succeeds Col. James E. Ash, United States Army Medical Corps (Ret.), who is retiring from active participation in registries.

Elexious T. Bell, professor of pathology at the University of Minnesota Medical School, Minneapolis, retired June 15. He has served the university since 1910, teaching first anatomy and since 1911 pathology. He was appointed head of the department in 1921. An advisory committee has recommended the establishment of a fund of $100,000 to create and maintain for teaching and research a museum of pathology in the medical school, which will bear his name. James S. McCartney Jr. is chairman of the E. T. Bell Fund Committee.

Richard H. Shryock, Ph.D., professor of American history and since 1938 lecturer in medical history at the University of Pennsylvania, Philadelphia, has been appointed director of the Institute of the History of Medicine and William H. Welch professor of the history of medicine at the Johns Hopkins University School of Medicine, Baltimore. The new director will assume his duties in September. The Institute of the History of Medicine was founded by Dr. William H. Welch in 1926. Dr. Welch, the first director, was followed by Dr. Henry Sigerist. Dr. Shryock became interested in medical history while serving with the Medical Corps during World War I. Returning to the University of Pennsylvania after the war, he continued training for the degree of Doctor of Philosophy.

Prizes, Awards, Etc.—According to the *Journal of the American Medical Association* a David Anderson-Berry silver-gilt medal, together with a sum of money amounting to about 100 pounds, will be awarded in 1950 by the Royal Society of Edinburgh to the person who in the opinion of the Council has recently produced the best work concerning the therapeutic effect of roentgen rays on human diseases. Applications for this prize are invited. They may be based on both published and unpublished work and should be accompanied by copies of relevant papers. Applications must be in the hands of the General Secretary, Royal Society of Edinburgh, 22 George Street, Edinburgh 2, by March 31, 1950.

Fellowships.—The American Cancer Society, in conjunction with the British Empire Cancer Campaign, announces a number of British American Exchange Fellowships in Cancer Research. These fellowships are open to American citizens who possess the degree of M.D., Ph.D. or D.Sc. and will provide specialized training in Great Britain; an equal number of young British scientists will be selected for training in this country. The fellowships, to be awarded by the society on recommendation of the Committee on Growth of the National Research Council, will be granted for a period of one year at $4,020, with travel allowance of $600. Applications may be procured from the Executive Secretary of the Committee on Growth, Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C.

Society News.—The 1950 meetings of the American Assocaition of Pathologists and Bacteriologists will be held at the University of Wisconsin, Madison, April 14 and 15, 1950.

The nineteenth annual meeting of the Biological Photographic Association, Inc., will be held in Cleveland on Wednesday, Sept. 7, 1949 through Saturday noon Sept. 10, 1949 at the Hotel Cleveland.

Books Received

Oral Anatomy. By Harry Sicher, M.D., professor of anatomy and histology, Loyola University School of Dentistry (Chicago College of Dental Surgery). Pp. 529, with 310 illustrations (24 in color). Price, $15. St. Louis: C. V. Mosby Company, 1949.

This book is dedicated to the memory of Julius Tandler (1869-1936), formerly professor of anatomy at the University of Vienna, Austria, and shows as its frontispiece a medallion portrait of the head of that eminent teacher. As is stated in the preface, the book is based on a German text written by Sicher in collaboration with Tandler (Sicher and Tandler: Anatomie für Zahnärzte, Berlin, Julius Springer, 1928). Though much of the book represents a translation of that text, and about 250 of the 310 figures are either from it or from Tandler's "Lehrbuch der systematischen Anatomie" (Tandler: Lehrbuch der systematischen Anatomie, Leipzig, F. C. W. Vogel, 1923-1929, vol. 4), there are some added sections, especially those dealing with the more recent observations on the growth of the skull and that of the alveoli in relation to the teeth, and there are about 35 new illustrations. The remainder of the figures were taken from previous publications by various authors. There is a failure to give parenthetically in the explanation of the figures either the titles of the bibliographic references or their place and date of publication.

As Sicher observes rightly, one of the most difficult problems of teaching anatomy or other basic sciences is that of correlation. Largely because of the arrangement of the curriculum, most students in a dental school—and in some medical schools—do not become aware of the applicability of theory to practice. When the student takes his course in anatomy he cannot apply his knowledge because he has not yet had an insight into the clinical problems in which anatomic knowledge is indispensable, and when later he starts his clinical training he cannot apply his anatomic knowledge because he has forgotten most of it. Since time is short, a review of anatomic details in a course of applied anatomy is then almost impossible; consequently "clinical teaching and learning are more and more mechanized and the student arrives at the conclusion that he can become a successful dentist without much knowledge in basic sciences." Sicher's book tries to bridge the gap between theory and practice. It endeavors not only to replace selected chapters of a textbook of anatomy in the freshman course but also to accompany the student through his clinical years by serving as a basic introduction to some of the practical courses. The book is intended to supplement textbooks on human anatomy, which are written primarily for use in medical schools, and the chapters of which dealing with the head and neck are at the same time too broad and not deep or special enough for the dentist or the oral surgeon.

The subject matter of the book is arranged in two parts: the first, *descriptive anatomy* of the regional divisions, and the second, *regional and applied anatomy*, in which the principle of arrangement is the clinic. The seven chapters of the first part deal respectively with (1) the skull, (2) the muscles of the head and neck, (3) the temporomandibular articulation, (4) the viscera, (5) the blood vessels, (6) the lymphatic system and (7) the nerves of the head and neck. The eight chapters of the second part are designated as follows: (1) palpability of the facial skeleton, (2) structure and relations of the alveolar processes, (3) anatomy of local anesthesia, (4) arterial hemorrhages and ligation of arteries, (5) the propa-

gation of dental infections, (6) tracheotomy and laryngotomy, (7) the temporomandibular articulation and (8) the edentulous mouth. Though the treatment of the subject matter is chiefly gross-anatomic, there is in chapter 1 an excellent section on the growth of the skull, including facial growth in relation to tooth eruption. The gross histologic details of the relations of the teeth to the tissues of their sockets also are well shown. The functional anatomy of the temporomandibular articulation and the muscles of mastication is considered adequately, but not so that of the other parts.

Since one of the merits of the book is the large number of illustrations, it is unfortunate that the figures, which were so excellent in the German text, so greatly lost their crispness and distinctiveness during the process of reproduction in this American text. It is generally a mistake to photograph half-tone figures and to prepare new half-tone etchings from them instead of using the original clichés (which in this case obviously was impossible); the contrasts between the highlights and the shadows are flattened. A grave error which the author and the publisher could have avoided, if they had been alert, is the different reductions during the reproduction of the figures. It is disconcerting when the various views of the skull and the different bones of the same skull are not shown in a constant size relation to each other. This oversight, the reviewer believes, has definitely impaired the quality of the book. Another criticism which may be leveled at many morphologists is their failure to indicate either the enlargement or the diminution of the actual view of the structure shown where an indication of the size relations is important for comparison. For none of the photomicrographs, for example, has Sicher expressed the magnifications employed.

The text is presented in a straightforward and matter-of-fact style. What it may lack in fluency, it gains in clarity, precision and simplicity of expression, which must be the dominant aim of the morphologist in his descriptions.

All in all, the reviewer regards Dr. Sicher's "Oral Anatomy" as the best book of its kind in English, and he congratulates both the author and the publisher for their achievement.

THE CHEMISTRY AND TECHNOLOGY OF ENZYMES. By Henry Tauber, Ph.D. Pp. 550, with 56 illustrations. Price, $7.50. New York: John Wiley & Sons (London: Chapman & Hall), 1949.

This book is an expansion of an earlier work, "Enzyme Technology," by the same author, and, as the title implies, it is divided into two sections: one on the general chemistry of enzymes and the second on the applications of enzymology to technology. The first section can be recommended as a useful guide to the chemistry of enzymes for the experimental pathologist. In addition to a generally orthodox classification of known enzymes and discussion of their properties it includes reasonably complete instructions for determination of a few of the more commonly measured and more easily measurable enzymes. This section will serve its most useful purpose as a guide to the literature since it is extensively documented. Its usefulness could perhaps have been extended by the inclusion of a more comprehensive section on enzyme kinetics and the fundamental considerations involved in devising a quantitative assay procedure for measuring enzyme activity. Present day enzyme research is striving for the recognition of the action of individual enzymes in organized reaction systems. There is little discussion in the book of enzyme systems such as those involved in glycolysis, urea formation, etc. Although such discussion more properly is a matter of the

biochemistry of intermediary metabolism, perhaps a chapter devoted to outlining a few systems would give a more dynamic conception of the action of enzymes.

The reviewer does not feel competent to judge the section on enzyme technology, a subject which is perhaps of less interest to the experimental pathologist. It will suffice to list a few of the subjects covered: Industrial production of yeast, ethyl alcohol by fermentation, brewing, production of antibiotics, baking processes, dairy technology, food preservation and tanning. Some material on microbiologic assay of certain vitamins and amino acids is included and should prove useful as orientation.

On the whole, the reviewer feels that this book, considering only the section on chemistry of enzymes, is not as useful a general text as "Chemistry and Methods of Enzymes," by Sumner and Somers, for the nonchemist research worker in the medical sciences. This opinion does not reflect on Dr. Tauber's effort, since he obviously has written the book for a different audience.

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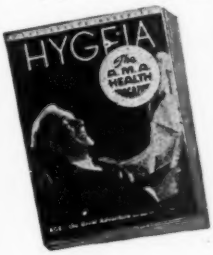

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